FEEBLENESS OF GROWTH AND CONGENITAL DWARFISM

MURK JANSEN

OXFORD MEDICAL PUBLICATIONS

OXFORD MEDICAL PUBLICATIONS

FEEBLENESS OF GROWTH AND CONGENITAL DWARFISM

PUBLISHED BY THE JOINT COMMITTEE OF
HENRY FROWDE AND HODDER & STOUGHTON
17, WARWICK SQUARE, NEWGATE STREET,
LONDON, E.C. 4

OXFORD MEDICAL PUBLICATIONS

FEEBLENESS OF GROWTH AND CONGENITAL DWARFISM

WITH SPECIAL REFERENCE TO DYSOSTOSIS CLEIDO-CRANIALIS

BY

DR. MURK JANSEN, O.B.E.

LECTURER ON ORTHOPÆDIC SURGERY, UNIVERSITY OF LEIDEN, HOLLAND

LONDON

HENRY FROWDE
OXFORD UNIVERSITY PRESS

HODDER & STOUGHTON
WARWICK SQUARE, E C. 4

1921

PRINTED IN GREAT BRITAIN BY R. CLAY AND SONS, LTD.
BRUNSWICK STREET, STAMFORD STREET, S.E. 1, AND BUNGAY, SUFFOLK.

PREFACE

THE microscopical photographs in the first part of this book have been made by the generous help of Dr. J. W. C. Goethart. To him and to Prof. R. de Josselin de Jong, who on our request kindly furnished the material for them, and to Prof. L. Polak Daniels, who in his rare spare hours found the time to make the microscopical preparations for me, I beg to tender my best thanks.

M. J.

December, 1920.

INTRODUCTORY NOTE

When studying the nature and the cause of "Achondroplasia" in 1910, I came to the conclusion that two principles, which had hitherto passed unnoticed, were underlying the facts, viz.:

(1) *Injurious agents affecting growing cell-groups enfeeble their power of growth.*

(2) *The measure in which growth is enfeebled is proportional to the rapidity of growth (which I termed "law of the vulnerability of fast-growing cell-groups").*

The whole of this book is an attempt to work out these principles.

It is to bring forward grounds for the assumption that the similarity between "Rachitis" and "Achondroplasia" is determined by these two principles, and that a number of other conditions, developing before or after birth and showing far less likeness, are yet linked together by the operation of the same principles.

In the first part growth-changes will be dealt with which are seen to develop after birth. In the second part congenital changes will be discussed. The latter will, upon the whole, appear to be more serious than the former.

The symptoms of the first part are more generally known, and, by their extremely high frequency, accessible for study to every practitioner; whereas the congenital growth-changes of the second part are often incompatible with extra-uterine life, and therefore come into contact with the practitioner not nearly so much as with the pathologist.

M. J.

December, 1920.

CONTENTS

PART II

CONGENITAL DWARFISM

FOREWORD

PHYSICAL science has risen from empiricism to its present height by the discovery of laws or parallelisms which are visible to the mental eye only, and when they are grouped and co-related they create order out of the seeming chaos which Nature presents. Natural laws are founded on the observation and explanation of the sequence of phenomena. In Biology a few general laws have been formulated, but Pathology and Medicine are unfortunately still largely in their empirical stage. They are waiting for laws to lift them to a higher plane.

This book aims at establishing principles explaining the manner in which body growth is affected by injurious influences. These principles have hitherto been ignored by text-books of pathology, and growth changes are described under different headings and by different names without co-relation and without a recognition of their real nature. The Author discusses the influences of pathological changes and those of pressure upon the determination of deformity. The aim of the Author has been to select what he terms "quantitative" changes of growth from pathology, uniting them into a new chapter and linking them together by simple laws or rules. He then clarifies the nature and cause of weakness of the musculature, of excessive height in adolescents and adults who have "outgrown their strength," of rickets and other conditions which appear as growth changes differing only in intensity.

He thus gives us a standard for judging the "constitution" of men from size, form, attitude and gait, from the condition of their hands and feet; and the insight into the causes of these defects provides us with principles to cultivate strength in future generations. He arranges into chronological order, by the application of the same principles, a number of congenital malformations whose nature and causes have always been considered obscure.

Moreover, the enhanced sensibility and fatigability of bone cells in which the quantitative growth changes are characterised yield a suggestion to the neurologist. To the orthopædic surgeon this work is an earnest endeavour to display the laws and rules by which a large number of deformities are determined and, in some cases, also the means by which they may be forestalled.

It is a privilege to have been asked to write a foreword to this philosophic and suggestive contribution. It carries a torch into the dark places and displays a new line of research both fascinating and scientific, and of great social and practical promise. The Author is known to us all as an orthopædic surgeon of international reputation, and his logical and painstaking methods of research should prove an inspiration and a model to colleagues the world over. It is not so well known that we as a nation are deeply indebted to Murk Jansen for his sympathetic—I may say, fraternal care of our sailors and soldiers interned in Holland.

ROBERT JONES.

Liverpool.

PART I

FEEBLENESS OF GROWTH

INTRODUCTION TO THE FIRST PART

Clinicians of all ages have drawn a distinction between "Disease" and "Feebleness," so much so that they have been in the habit of saying that the disease is cured and feebleness is the cause of death. They have studied the feebleness of certain organs by the changes that have taken place in their functions. But the feebleness of one of the most important among the functions of the organism, viz. that of growth, has been almost completely neglected. An opinion seems even to prevail among pathologists that a growing subject may come under the influence of an injurious agent without his growth being affected.

In the present study we have tried to supply this deficiency by studying the manner in which injurious influences will affect the growth of the individual. The knowledge of this will teach us how to infer from the body-height, form, attitude, gait and other signs in the adult to what extent he has been affected by the operation of injurious agents during the period of his growth.

Clinicians and pathologists have indeed observed the symptoms which we have ranged amongst those of feebleness of growth, and have described them under different names, mostly derived from the Greek and ending in "itis," "ism" or "osis," and as crases, diatheses, status, habitus or anomalies of the constitution. Their nature and their relation to the normal condition, however, have not been specified. In the present study, therefore, we shall describe no new symptoms. We shall only try to indicate the relation of certain well-known phenomena to the normal condition, as well as the rules according to which they evolve from the normal state.

DEFINITION OF FEEBLENESS OF GROWTH

In order properly to explain the nature of the changes we have in view, let us imagine a child which is affected by a focus of microbic infection. This focus—if serious enough—will render the child "ill," and will provoke *qualitative* changes, which may even be specific for the microbe in question. It is not to these facts, already much studied, that we wish to direct attention; but to the fact that the child, in addition to manifesting

	No. 1.	No. 2.	No. 3.
Age . .	17 years 1 month.	15 years 4 months.	12 years 10 months.
Height . .	1·705 m.	1·495 m.	1·365 m.
Weight . .	56·7 kg.	46 kg.	37·2 kg.

Height = the normal of Quetelet	+ 9·6%	+ 1·28%	+ 0·5%
Weight = the normal of Quetelet	+ 14·8%	+ 16%	+ 30%
Began to walk at the age of	2 years.	2 years.	2 years.

FIG. 1.—THE FAMILY H.
Height of Father 1·70 m.,

No. 4.	No. 5.	No. 6.
10 years 1 month.	7 years 6 months.	5 years 1 month.
1·30 m.	0·935 m.	0·775 m.
26·7 kg.	13·6 kg.	10·4 kg.

+ 5·8%	− 11·4%	− 14·8%
+ 25·5%	− 5·4%	− 19·4%
2 years.	5½ years	not yet (5 years).

(January 7, 1917.)
of Mother 1·58 m.

these qualitative changes, becomes feeble. All organs, even those not directly affected, and their functions, show signs of feebleness; and so it is with the important function of growth. This also is affected by feebleness, and it is with this *feebleness of growth* that we intend to deal. Whilst diseases manifest themselves under an infinite number of forms, the feebleness of growth which they produce is essentially the same for every degree of it. The various degrees of feebleness of growth, indeed, differ mutually; but the symptoms of the same degree hardly differ. It little matters whether they have been provoked by enteritis or pneumonia, whooping-cough or some other infection after birth, or by some injurious agent operating before birth, *e. g.* great fatigues of the mother during pregnancy. Every nocivity acting on a growing body, whatever be its nature, weakens its power of growth, provided the nocive agent be of sufficient intensity. Feebleness of growth, therefore, depends rather upon the intensity than upon the quality of the nocivity.

It is evident that the changes in the human body must be either qualitative or quantitative. Now those which are occasioned by disease may be qualitative, as, for example, the changes of the serum in infectious conditions, whilst feebleness of growth is to be ranged among the *quantitative changes* of the processes of life.

METHOD OF SEEKING THE SYMPTOMS OF FEEBLENESS OF GROWTH

The seeking of the symptoms of feebleness of growth is based on the comparison of children of the same parents—preferably in the case of large families—with regard to the injurious influences to which they have been subjected.

It is obvious that in carrying out this comparison we meet also with hereditary phenomena which are purely qualitative in nature. These, however, are distributed among the different children in an absolutely arbitrary manner, largely following the laws laid down by Mendel. Nos. 1 and 5 of a family, for instance, may have the dark eyes of the father, whilst the rest possess the blue eyes of the mother. But with such phenomena as these we are not dealing at present; they can be easily distinguished from feebleness of growth. Instead of showing an exact parallelism with the injurious influences by which the children have been affected, these purely hereditary phenomena never yet have shown any such parallelism. Thus it will be easy to allow for them in the following observations.

Obstetricians have observed that the second child of a mother, as

well as those that follow, may develop better than the first. In general, however, the children of the same parents may be expected to show a great resemblance in their development. But if injurious influences have been acting on some of the children, either before or after birth, characteristic phenomena present themselves which vary with the intensity of the nocive agent rather than with its nature. It is this series we are about to describe as illustrative of feebleness of growth. They will be found to be governed by three fundamental principles.

THREE FUNDAMENTAL PRINCIPLES OF FEEBLENESS OF GROWTH

I. *Feebleness of growth is proportional to the intensity of the nocivity.*

II. *Feebleness of growth is proportional to the rapidity of the growth of the individual and its parts* (Law of the Vulnerability of Fast-growing Cell-groups).[1]

III. *Feebleness of growth is characterized by enhanced sensibility and enhanced fatigability.*

In the following sections we will try to illustrate the operation of these principles, and, with that in view, shall first trace the symptoms of feebleness of growth.

THE SYMPTOMS OF FEEBLENESS OF GROWTH

For reasons which will become apparent later on (cf. p. 19), the series of symptoms of feebleness of growth is best studied in families in which the only nocivity traceable is fatigue of the mother during pregnancy, whilst nutritive, toxic or infectious agents are excluded. We will give some examples of such cases.

In the family H. (see Fig. 1) there are no infectious or nutritive nocivities to be traced, only that, as in all poor families, the fatigue of the mother has increased in successive pregnancies. Of her own accord she has informed us that during her fifth and sixth pregnancies she often used to fall down on the floor from fatigue.

The body-height of the first child is 9·6 per cent. above the normal, and even surpasses that of his parents. That of Nos. 2, 3 and 4 is about equal to normal, whilst that of Nos. 5 and 6 is 11·4 per cent. and 14·8 per cent. respectively below the normal. This retardation of growth becomes obvious when we compare No. 6 with a normal child of the same age (cf. Figs. 2 and 3).

[1] Cf. *On the Vulnerability of Fast-growing Cell-groups*, by the Author. International Congress of Medicine London, 1913.

The body-weight of Nos. 5 and 6 is 5·4 per cent. and 19·4 per cent. respectively below the normal, whilst the other children are above the

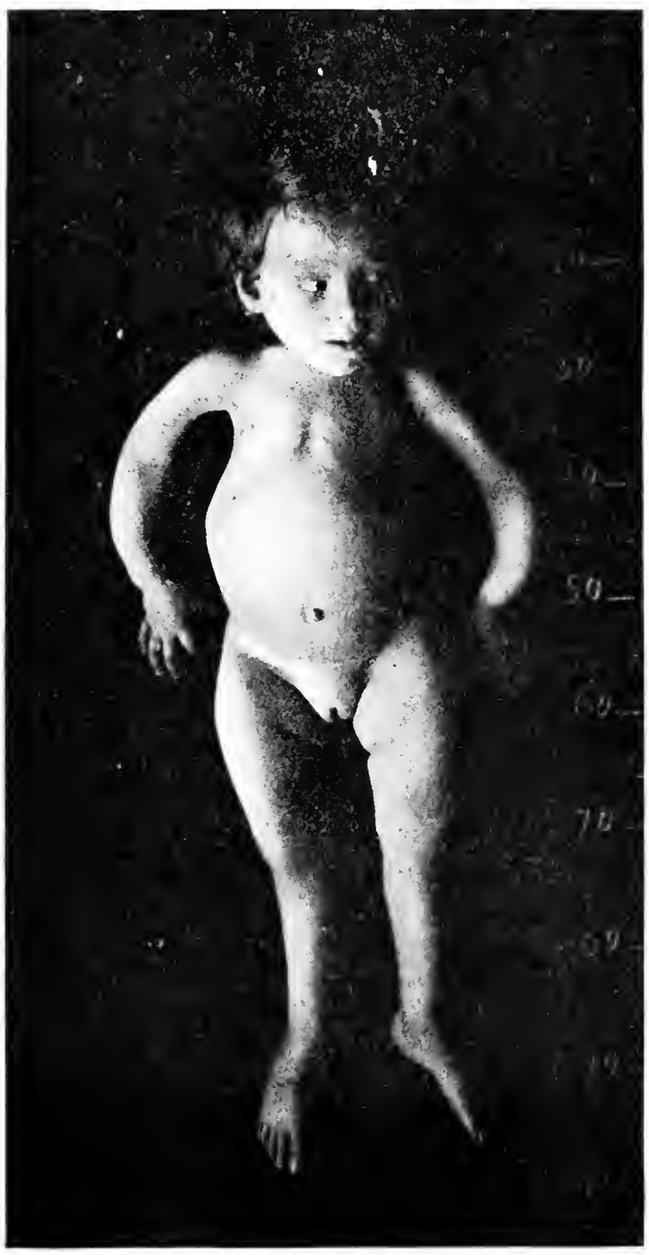


FIG. 2.—Cat. H. 5 years 8 months.

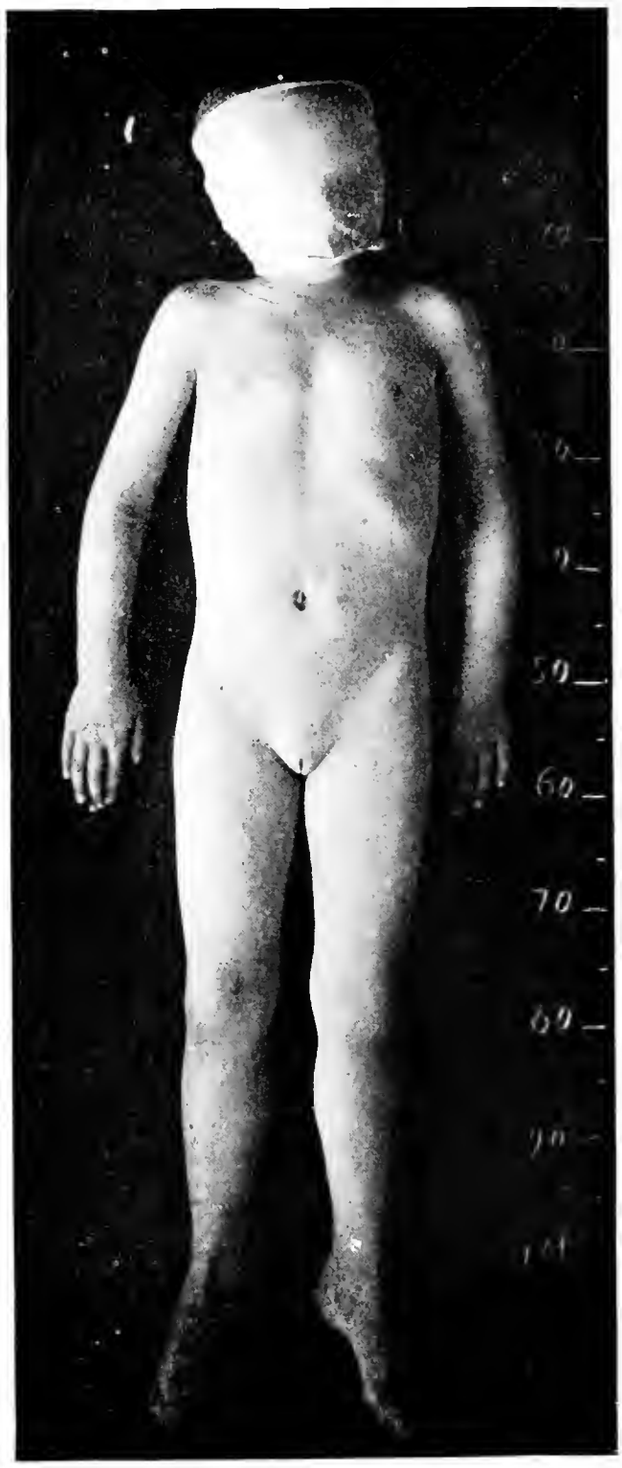


FIG. 3.—Soph. F. 5 years 6 months.

normal body-weight. The two youngest children learned to walk at the age of five and a half and seven and a half years, whilst the others walked when they were two, the development of the locomotor apparatus

of the two youngest children taking place much later than that of the others.

Every clinician, seeing the two youngest children, would, in conformity with the science of our days, label this condition Rachitis. But we shall try to show in the following pages that Rachitis is just a severe degree of feebleness of growth, conditioned, like the other degrees, by the principles we have just formulated. To that effect we will consider more closely the different changes of normal growth with which we are dealing.

The eldest child exceeds normal height as we have observed. We might be tempted to assume that this was the outcome of a surplus of the power of growth. But this is not the case: the boy's *muscles are too weak*. He has flat feet, a protuberant abdomen, a round back, blue and moist hands (acrocyanosis and acrohyperhydrosis). These *four muscular symptoms* prove that his musculature is too feebly developed to bear the body-weight, to resist abdominal pressure, to balance the respiratory forces, or properly to resist hæmostatic pressure. Briefly, the eldest child *has outgrown his strength*.

Nos. 2, 3 and 4 equally show the four muscular symptoms. No. 4 has, in addition, developed knock-knees, showing that in her the growth of the skeleton is altered in those parts which find themselves in the most rapid growth, viz. the growth-cartilages near the knee. This girl has weak feet like her brothers. There is no doubt but that in the upright attitude the cartilages near the knee are made to bear greater pressure in the lateral than in the medial parts. To this greater pressure they have responded with lessened growth.—In the normal condition the reverse takes place, for the part bearing more weight shows a more rapid growth. From this fact the normal course of development is for the curved legs of little children to grow straight and to remain straight. In other words *growth-cartilages normally have a reserve power of growth*. This reserve power of growth has disappeared in No. 4.

Later on we shall consider this phenomenon more closely (cf. p. 37 ff.). For the present it may suffice to emphasize the fact that in No. 4 there is a *retardation of growth* as the result of *an increase of pressure*, viz. in the fastest growing skeletal parts. And the same phenomenon will be observed in the more severe cases of feebleness of growth even in parts growing less rapidly (p. 10).

Nos. 2, 3 and 4 are examples of *the common type of knock-kneed children* which has been the subject of many disputes as to whether they are or are not to be reckoned among the "rachitic." These children *constitute an intermediate stage* between the type with muscular weakness which has outgrown its strength, represented by No. 1, and the type whose body-height lags behind the normal, and which is represented by Nos. 5

and 6. In other words: *between the slight degree of feebleness of growth, which chiefly affects the muscles, and the severe degree which moreover affects all skeletal parts.* The characteristic thickenings which are visible in all growth-cartilages of Nos. 5 and 6 are palpable in the ribs and the lower ends of the fibula in children of this type. The meaning of these diaphyseo-epiphyseal thickenings will be discussed in one of the following sections (see p. 21 ff.).

We have seen that in the knock-kneed child the retardation of growth from increase of pressure shows itself only in the neighbourhood of the growth-cartilages near the knee. In Nos. 5 and 6 this retardation of growth, owing to increase of pressure, is manifest near all growth-cartilages. The smallness of No. 6 of the family H. (cf. Figs. 2 and 3) shows, as we have seen, that in all growth-cartilages growth is retarded. But the deformity which presents itself near each of these cartilages shows that growth has been retarded in different degrees in the different parts of these cartilages. Wherever different parts of these cartilages have been subjected to varying degrees of pressure, growth has been retarded in proportion to the pressure to which the parts have been exposed. This holds good for the growth-cartilages of the vertebræ, as well as for those of the long bones. Nos. 5 and 6 thus constitute the type predisposed to develop deformities of all bones—of the spine and chest as well as of the extremities. Moreover, the diaphyses are curved. The diaphyses normally find themselves in less rapid growth than the growth-cartilages (cf. pp. 11 and 12), and in severe degrees of feebleness of growth they also seem to show a retardation of growth which is accentuated on the side that is most exposed to muscular pressure. The postero-internal side of the femur, for example, become concave under the stress of the adductors and long flexors of the thigh, these muscles being to the femur as the string is to the bow. For this reason they have a greater tendency to bend it than has the quadriceps muscle, three heads of which have their origin in various parts of the femoral surface.

The formation of knock-knees and of diaphyseal bendings has often been considered as due merely to fracture; but it should be observed that fractures imply angular deformity, quite different from the diaphyseal curves under consideration. Moreover, they involve sudden onset, loss of function and pain, all of which conditions are absent in diaphyseal curves and in knock-knees.

Compression of cartilage or pre-formed bone, however, apart from any growth, may have a share in the production of these deformities. In a study, "On Bone Formation,"[1] we have brought forward reasons

[1] *On Bone Formation: its Relation to Tension and Pressure*, by the Author. Manchester University Press, 1920.

favouring the assumption that bone made to bear—either relatively or absolutely—too much weight, first shows an absorption of the lime salts, and next undergoes compression. Hence it would be difficult to deny to this process of compression a share in the production of diaphyseal bendings as well as of knock-knees. It might be even contended that excess of pressure affected pre-formed bone only and never interfered with the rapidity of growth in the diaphyseo-epiphyseal discs. But this could only be upheld if functional pressure were no stimulus for bone growth. We know, however, that it is (cf. p. 36); and it is safe to assume that the stimulus which is able to accelerate growth is, under suitable circumstances, also able to retard it. These circumstances will be further studied in the course of this monograph. And if in preceding paragraphs, as in the following pages, we neglect the factor of compression of pre-formed bone or cartilage, it is because this makes no essential difference as regards the conclusions arrived at.

In a striking way *this retardation of growth in response to increase of pressure* shows itself on a comparison of the skiagrams of the hand of No. 6 of the family H. with those of the (very nearly) normal child of Fig. 3 (see Figs. 4 and 5). The hand of Fig. 5 is reproduced of three-quarter normal size; that of Fig. 4 is reproduced of a size such as to make the median ray, measured from the base of the third metacarpal bone to the end of the terminal phalanx, equal to the normal hand. Its size is about 0·92 of the normal. What strikes us on comparing these two figures is that in the rachitic hand the metacarpals are too short, the fingers relatively too long. And among the metacarpals the first and fifth are still more retarded than the others. So the bones of the hand of No. 6 of the family H. show a retardation of growth which is proportional to the pressure they have to resist. The metacarpals, which are subjected to greater pressure than the fingers, show more retardation of growth; and the first and fifth of these bones, which, moreover, have to bear the pressure of the thenar and hypothenar muscles, appear also to experience the inhibitory effect of their action. It should be observed that the shortening of these metacarpals is not due to bending. The bones of this hand show a diminution of the normal power of bones to grow against pressure. In No. 4 of the family H. this diminution of growth is limited to a pressure which surpasses the normal, while in Nos. 5 and 6 it shows itself even when the pressure is below the normal.

The transverse dimensions of the metacarpals show no diminution. As is well known, periosteal bone is formed in membrane. The formation of membranous bone may be considered as a less elaborate process than that of bone formed in cartilage such as we find in the growth-cartilages.

Moreover, as Hunter has demonstrated, on the outside of the diaphyses, while thickening, the whole of the periosteum contributes not only to the increase in girth of the bones but also to their increase in length, whilst in the interior at the ends it is the small number of cells in the

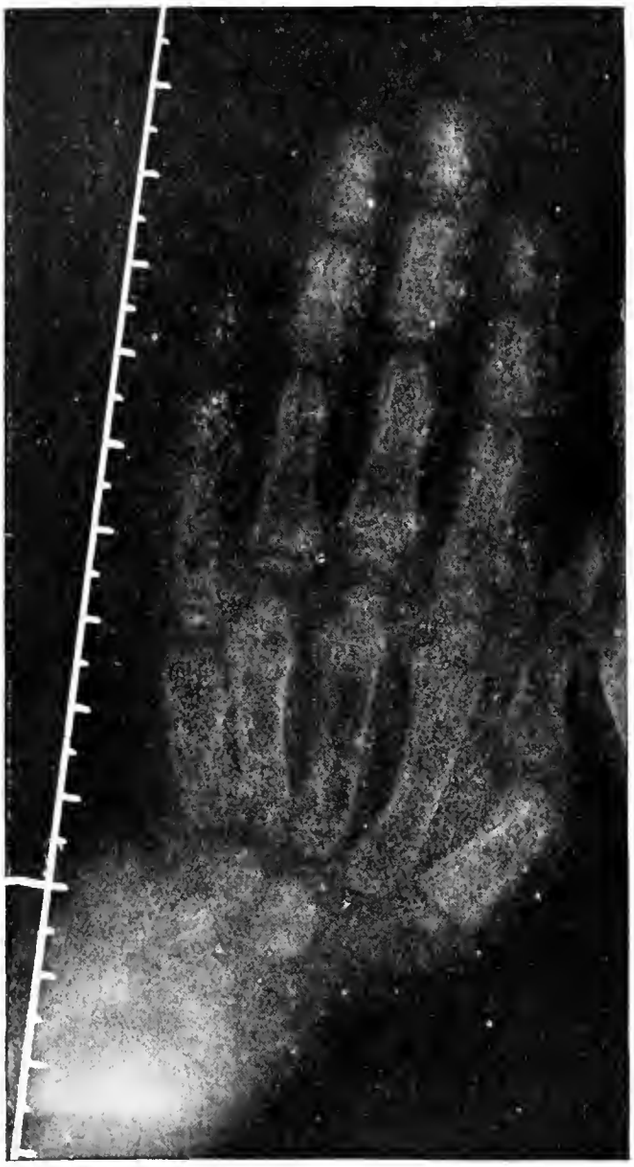


FIG. 4.—Cat. H.

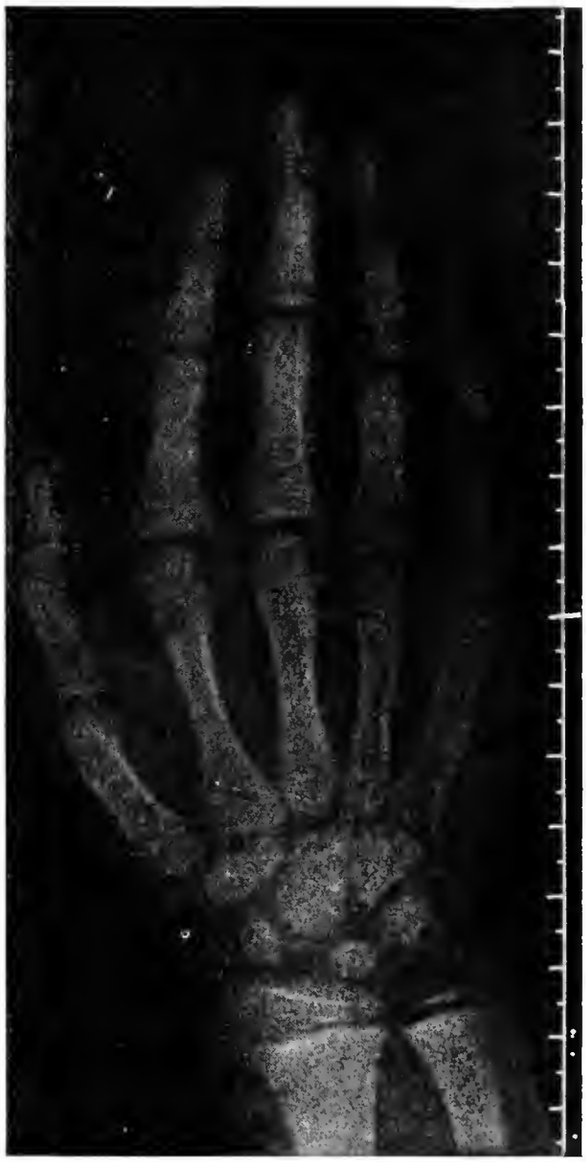


FIG. 5.—Soph. F.

growth-discs which provide this lengthening. And in these differences between the diaphyses and the growth-cartilages we shall later on recognize a cause of the difference of degree in which they are affected in feebleness of growth.

Comparison of the hands of Figs. 4 and 5 shows still another phenomenon which, though not unknown, has not hitherto attracted the attention it deserves. The bone centres of the epiphyses, as of the

carpal bones, are less developed in the hand with retarded growth than in the normal hand. All the bones, indeed, appear to contain less lime salts; but around the bone centres there remains a shell totally devoid of lime salts which, therefore, is still cartilaginous, and would have been ossified in normal conditions. On comparing the skiagram

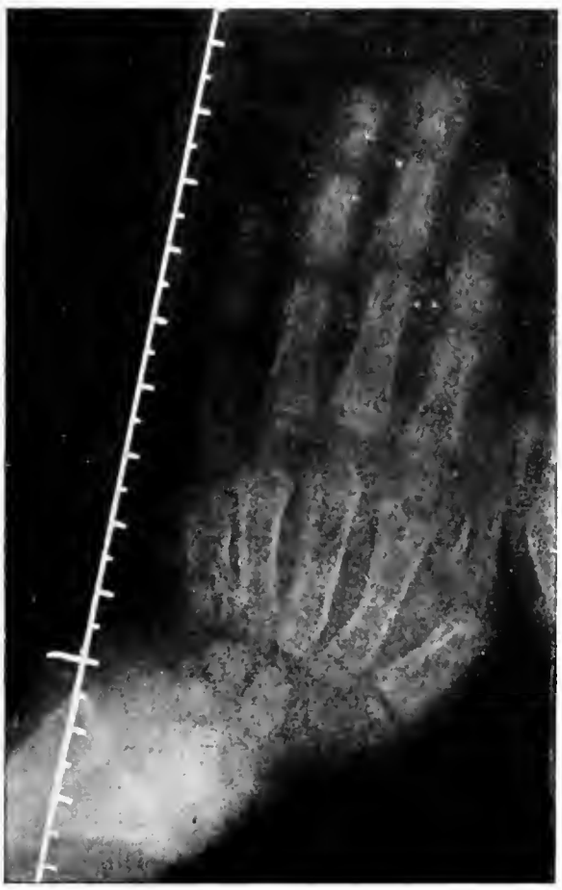


FIG. 6.

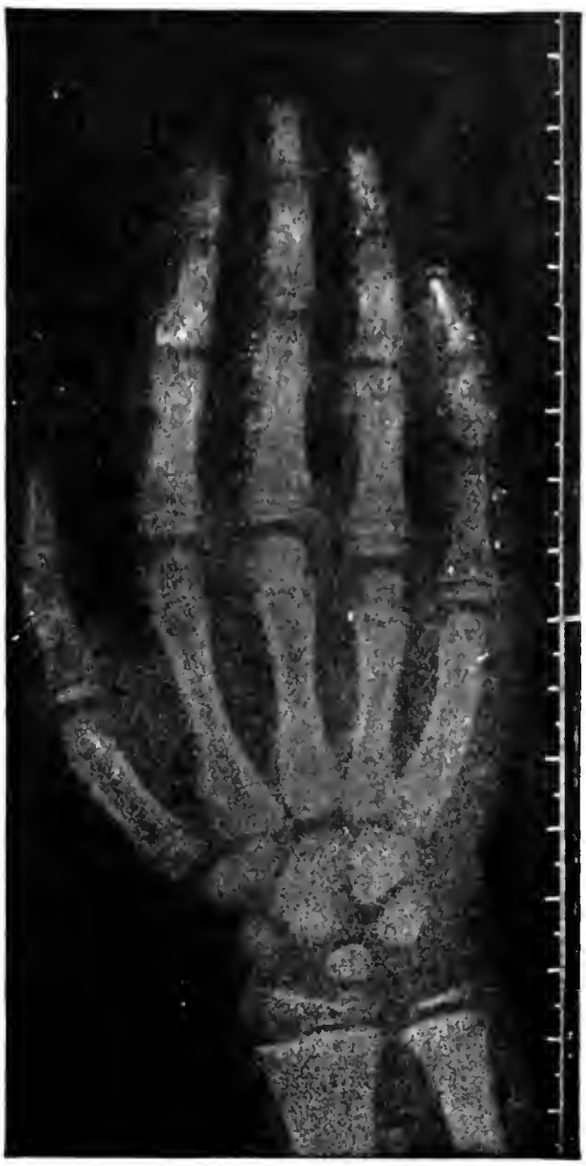


FIG. 7.

of the hand of No. 6 with that of the normal individual (*i. e.* the hand of Figs. 2 and 3), both now three-quarter normal size (see Figs. 6 and 7), it becomes evident that all the bones are too small; but the bone centres show still more retardation of growth. So while the growth of all skeletal parts of No. 6 has been retarded, ossification as such shows extra-retardation.

The same phenomenon presents itself on a comparison of the knees

of these children. The skiagrams of these knees are represented by Figs. 8 and 9, both half natural size.

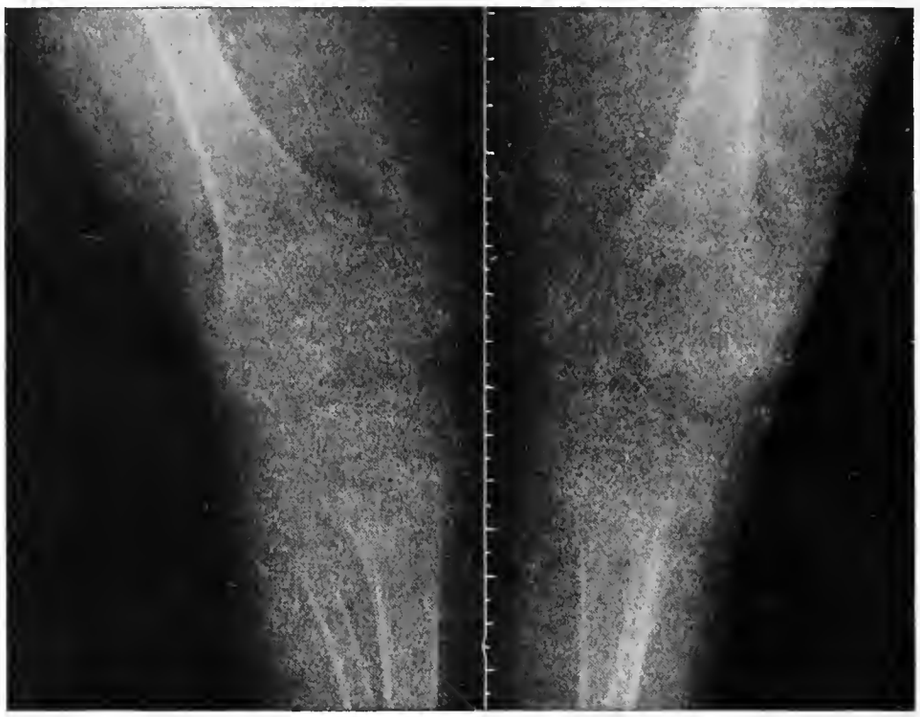


FIG. 8.—Cat. H. (Half natural size.)

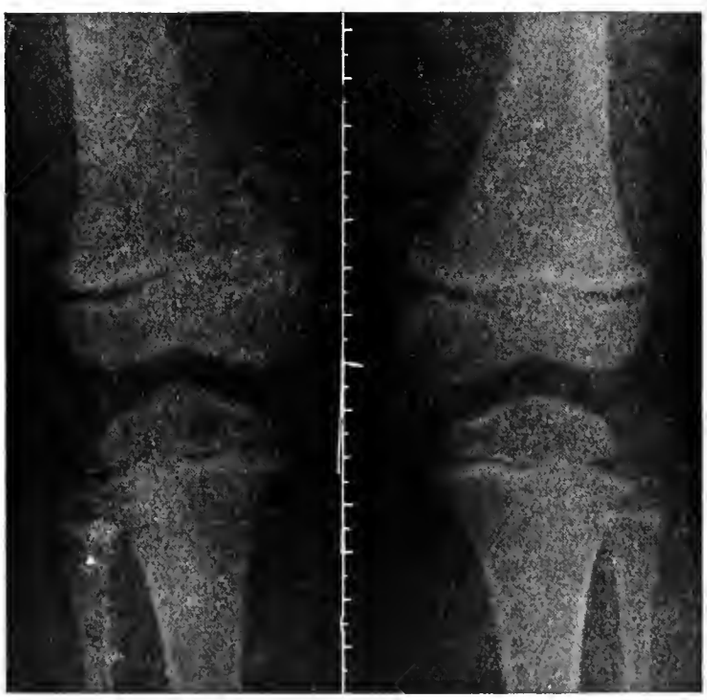
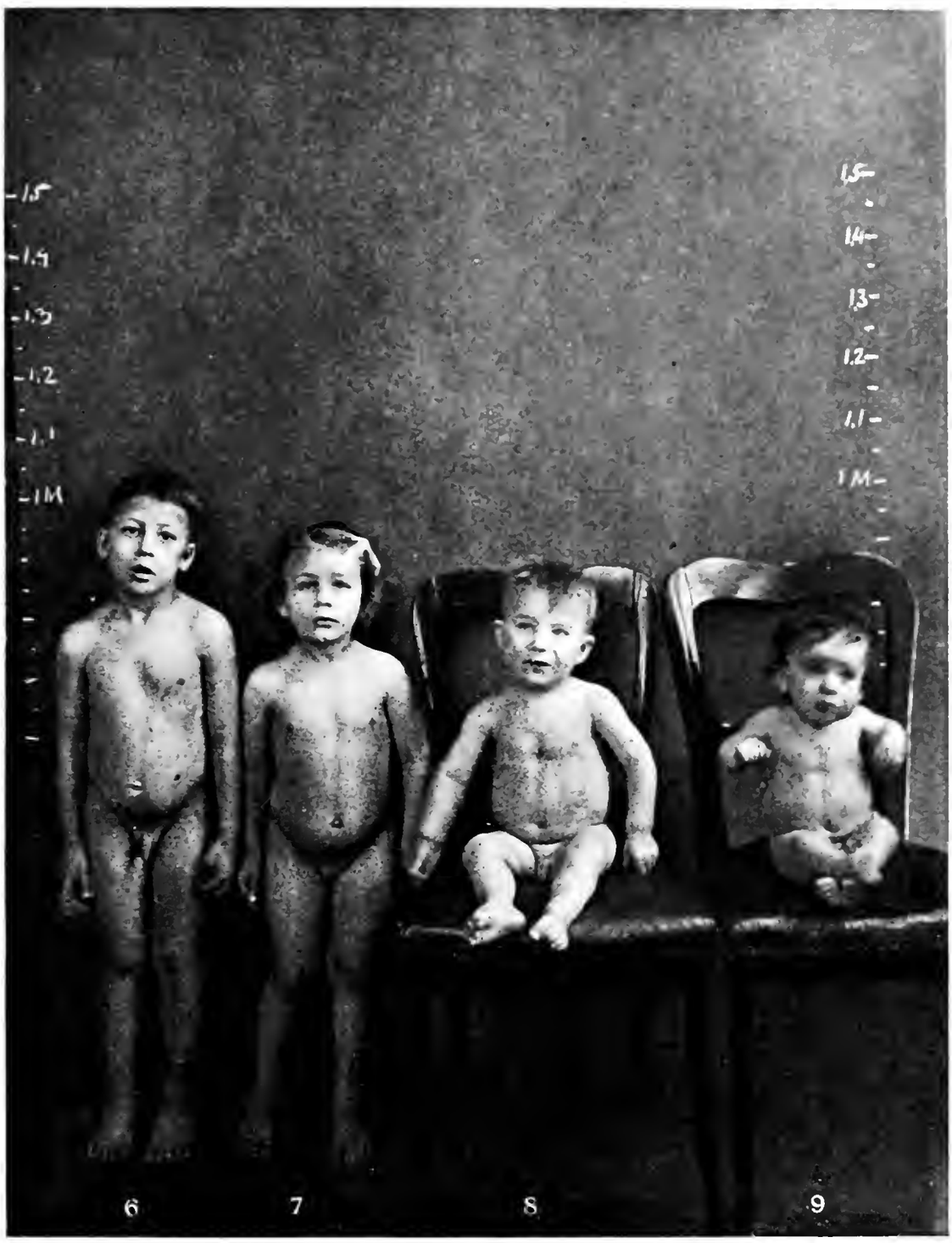


FIG. 9.—Soph. F. (Half natural size.)

And the extra-retardation of ossification as such will be shown to cause the thickening of the growth-cartilages, which we shall study in a separate section.

No. 6.	No. 7.	No. 8.	No. 9.
6 years 2 months.	5 years 1 month.	2 years 11 months.	1 year 8 months.
1·055 m.	0·963 m.	0·758 m.	0·631 m.
18·2 kg.	15·4 kg.	10·2 kg.	6·3 kg.



− 7·62% + 4%	− 1·6% + 5·8%	− 11·6% − 17%	− 14·4% − 38%
2 years.	2 years.	cannot stand up at the age of 2 years 11 months.	cannot stand up

Summing up, we find that the family H. has shown us three types:

(1) The type with weakness of muscles and enhanced body-height (the type which has outgrown its strength).

(2) The type with average height with muscular weakness and knock-knees.

(3) The type the height of which is below the normal, with thickened growth-cartilages and curved diaphyses—briefly, the rachitic type. It shows a retardation of the growth of the skeleton with an extra-retardation of cell-differentiation.

In the following chapters these three types will be shown to illustrate the three degrees of feebleness of growth, viz. *the slight degree, the moderate degree and the severe degree of feebleness of growth.* In them we find successively affected, first the musculature, next the growth-cartilages, and lastly also the diaphyses.

It is almost unnecessary to observe that in the youngest children the musculature is affected to a still greater extent than in the eldest: the extremities of the youngest are flaccid, the abdomen protrudes excessively, and when the child tries to get up from the lying position into the sitting attitude, the lateral parts of the abdomen show additional bulging in accordance with the insufficiency of the oblique and transverse abdominal muscles.

We do not meet with the three types of feebleness of growth mentioned in the above in all large families. In the family F. (Fig. 10), in which—as in the previous family—there is no nocive agent to be traced other than fatigue of the mother—increasing at each successive pregnancy—the five or seven first children all belong to the second type. Nos. 8 and 9 represent the third type; so in this family the first type, that of slight feebleness of growth, is missing.

I.—FEEBLENESS OF GROWTH PROPORTIONAL TO THE INTENSITY OF THE INJURIOUS AGENT

In the two families we have just considered there was a parallelism between the fatigue of the mother during pregnancy and the degree of feebleness of growth by which the various children were affected. In the third family which we represent (see Fig. 11), this parallelism between the intensity of the injurious agent and the degree of feebleness of growth is more obvious still. Note that all these children display muscular weakness. The abdominal protrusion shows a gradual increase from the eldest to the youngest. The three types of feebleness of growth just described are all represented in this family. Now, after

	No. 1.	No. 2.	No. 5.	No. 6.
Age . . .	13 yrs. 2 mths	11 yrs. 9 mths.	7 yrs. 9 mths.	6 yrs. 4 mths.
Height . .	1·51 m.	1·302 m.	1·191 m.	1·075 m.
Weight . .	35·2 kg.	24·7 kg.	21 kg.	16·7 kg.

Nos. 3 and 4 died 5 months and 3 weeks old.

Height = the normal of Quetelet	+ 5·8%	− 2·76%	+ 5·58%	+ 2·48%
Weight = the normal of Quetelet	+ 0·28%	− 14·5%	+ 12·3%	+ 1·2%
Began to walk at the age of	14 months	1½ years.	1½ years.	1½ years.

Nos. 3 and 4 died 5 months and 3 weeks old.

FIG. 11.—THE FAMILY V. d. H.
Height of Father 1·682 m.,

No. 7.	No. 8.	No. 9.
5 yrs.	3 yrs. 3 mths.	1 yr. 9 mths.
0·907 m.	0·775 m.	0·735 m.
11·5 kg.	10·5 kg.	10·7 kg.

— 8·1%	— 10·8%	— 4·3%
— 27·2%	— 13·2%	— 0·9%
3 years.	3 years.	Not yet. (Mother has taken rest the sixth month of pregnancy for appendicitis.)

(June 4, 1917).
of Mother 1·572 m.

No. 1, who is not below the normal, the height of No. 2 shows as much as 2·76 per cent. retardation. Nos. 3 and 4 died at the age of five months and three weeks respectively. So the mother (an energetic woman, who used to sit up late at night sewing in order to add to her husband's small income), was not disturbed in her scanty allowance of sleep by these children, nor did she have to look after them during her pregnancy with the fifth child, which is 5·58 per cent. above normal length; Nos. 6, 7 and 8 go on diminishing; the height of No. 6 being 2·48 per cent. above, that of Nos. 7 and 8 being 8·1 per cent. and 10·8 per cent. below the normal. No. 9, however, has grown better than the preceding children, for he is only 4·3 per cent. below normal height. Now the mother had to keep in bed during the sixth month of her pregnancy on account of appendicitis, and obviously the injurious effect of the inflammatory process upon her has done less harm to the fœtus than the rest she consequently enjoyed has benefited him.

We often meet with one child in a family with serious feebleness of growth among brothers and sisters that have grown better, where an injurious agent is traceable which has acted on that particular child. For instance, the first child of such a family, in which the other children had shown normal growth, displayed "rachitis." It was found that during her first pregnancy the mother had had to look after her doting father and three brothers, and then after her father had died and her three brothers had got married, children were born who showed normal growth.—Again, the third of five children had severe "rachitis," and during her pregnancy with that child the mother, it was found, had to nurse her husband, who was laid up in bed with typhoid fever, and had also to look after two little infants.

We have observed that when, after the birth of children with severe feebleness of growth, others are born, they often display practically no power of growth at all. They show "athrepsy," or "pædatrophy," or else they die young, or are born dead. Hence the "rachitic" deformed (for instance, the hump-backed) often have a history of brothers or sisters who died young. The hump-backed have, so to speak, had a narrow escape from death. Therefore to us *muscular weakness* (*attended by increased height*), *epiphyseal "rachitis," diaphyseal "rachitis," athrepsy and pædatrophy form an ascending series of degrees of feebleness of growth.*

It is almost superfluous to add that it is chiefly in the poorer classes that the severe forms of feebleness of growth are found. In better circumstanced families they are rare.

It must be emphasized that not only after fatigue undergone by the mother, but also after any other injurious agent, the same changes of growth are observed in the children. Sometimes there is a history of

persistent vomiting, hæmorrhages or diseases of the mother during pregnancy, sometimes of infections or intoxications of the child after birth. Whoever sees a child exemplifying one of the types of change of growth we have just described, among normal children of the same parents, and compares it with others with regard to injurious agents that have been acting, will as a rule be able to trace some special obnoxious influence that may be held responsible for the feebleness of growth of that particular child.

In the above we have restricted ourselves to representing families in which fatigue of the mother was the only injurious agent to be traced, because other injurious agents, *e. g.* infections, do not so well permit of the intensity of the nocivity being determined. We have avoided including cases of infection followed by feebleness of growth, because the susceptibility to the infection may be a qualitative change, varying with the subject, and thus may enter in a degree hardly to be determined into the series of causes of the disease and consequently of the feebleness of growth. In other words, in the case of infectious agents we are only very rarely able to determine how far the symptoms of feebleness of growth are to be considered as a result of the injurious agent and how far they should be considered as its cause.

II.—FEEBLENESS OF GROWTH PROPORTIONAL TO THE RAPIDITY OF GROWTH (BOTH OF THE PARTS AND OF THE INDIVIDUALS)

The question arises: Why do the injurious agents first affect the muscles and then also the skeleton?—The muscles constitute 25 per cent. of the body-weight in the new-born child, 43 per cent. in the adult. No tissue in the body, therefore, demands so much of the power of growth, and it is only rational that a lack of the power of growth should make itself first felt wheresoever the exigencies of growth are greatest. The law of the vulnerability of fast-growing cells, according to which the vulnerability of cells is proportional to the rapidity of their growth, therefore throws light upon the fact that feebleness of growth first manifests itself in the muscles. After the musculature, the skeleton demands most growth, for it forms 13·5 per cent. of the body-weight in the new-born child, and rises to 17·5 per cent. in the adult. Furthermore it is in harmony with the above law that in the skeleton the growth-cartilages are the first to be affected, while in the more severe cases the diaphyses follow. And in the choice of the growth-cartilages the organism shows its conformity to this law. It is generally known that in the second year of life—the time when the child begins to walk—

the legs lengthen more rapidly in proportion to the trunk. This continues up to adult age, and during these years the four growth-cartilages of femur and tibia add more to the height of the body than do the forty-eight growth-cartilages of the vertebræ. It is equally well known that this lengthening of the lower extremities is for the greater part achieved by the growth-cartilages near the knee. The rapidity of their growth therefore exceeds that of the vertebral growth-cartilages over twelve times. In harmony with this the fact presents itself that children with moderate feebleness of growth have a tendency to develop knock-knees, especially after they begin to walk. Before that time is the period when the growth of the trunk predominates, *i. e.* the time of the development of deformities of the ribs and the spine. And from these considerations it is pretty safe to lay down the rule that in the scoliotic or hump-backed with straight legs (*i. e.* without either knock-knees or bow-legs) the development of their lateral curvature dates back to the time before they had started to walk.

Be this as it may, in the localization of the symptoms of feebleness of growth we are struck by their parallelism with the rapidity of normal growth of the parts in question. And in the extra-retardation of cell differentiation, which we will deal with more at large in a separate section, this phase of growth is seen to be only a more elaborate process than that of cell-division and of cell-enlargement.

As with the intensity of the nocivity and with the rapidity of growth of the *parts*, the series of phenomena which we have termed feebleness of growth shows a parallelism with the rapidity of growth of the *individuals*. The normal rate of rapidity of growth, as is well known, slows down from the moment of birth. In the first, second and third years of life the body-weight increases 200 per cent., 20 or 30 per cent. and 15 per cent. respectively, the body-length 40 per cent., 13 per cent. and about 10 per cent. In the eighteenth year the body-weight increases only 5·2 per cent., and the height 2·6 per cent. In accordance with this, the severe forms of feebleness of growth belong to the first year of life, the slight forms to adolescence. The same nocivity, an intestinal catarrh, which will cause death or pædatrophy or athrepsy in the first year of life, may provoke diaphyseal or epiphyseal "rachitis" in the following years, muscular weakness—attended even by excess of body-height—during adolescence. *Hence the fact that the first year of life is characterized by high mortality and by pædatrophy or athrepsy, whilst the following years successively show a tendency toward diaphyseal rachitis, epiphyseal rachitis and muscular weakness with excess of height, is explained by the diminishing rapidity of growth of the individual,* i. e. *in view of the law of the vulnerability of fast-growing cell-groups.*

It stands to reason that this consideration holds good only in so far as the obnoxious agents do not diminish after birth.

In the same individual with feebleness of growth the above series of symptoms has a tendency to show itself in the different years of life successively. Adolescents with weakness of the musculature who have more or less outgrown their strength, may often be observed whose tibias as well as femurs prove that diaphyseal "rachitis" has existed in the first year of life. The severest cases of feebleness of growth, however, do not as a rule attain an excess of height during adolescence, and they mostly remain below normal height for the rest of their lives. Further observations, however, are needed to ascertain the exact course which feebleness of growth takes in post-natal life after the different nocivities that may have acted at different epochs of either pre- or post-natal life.

In view of the above considerations it might be imagined that the eldest children in the families we have represented, which show excess of body-height, may have been in the same condition as the younger ones when they were their age. This is not the case. They all started walking at the age of one and a half or two and a half, whereas the younger ones have learned to walk only much later. So the development of their locomotor apparatus has been retarded more; in other words, they exemplify a severer degree of feebleness of growth.

EXTRA-RETARDATION OF CELL-DIFFERENTIATION CAUSE OF THE THICKENING OF THE GROWTH-CARTILAGES

In order to justify an opinion regarding the nature of the thickening of the growth-cartilages, we have made a histological examination of the same rib in children who died at the same age from diseases of different nature and duration.

Figs. 12 and 13 represent two enlargements of this cartilage in a child one and a half years old which had died from acute broncho-pneumonia. They hardly differ from the normal condition.

As in the top of a growing plant, the normal growth-cartilage shows three well-defined stages one beside the other :

(1) That of *cell-division* (formation of new cells).

(2) That of *cell-enlargement*—where there is no division whatever—(columns of cartilage-cells).

(3) That of *cell-differentiation*—where there is neither division nor enlargement—(formation of bone-cells).

Fig. 12 shows these three stages of bone-growth.

Fig. 13 shows only the last two stages, more enlarged. The vascular loops are visible touching the cartilage-cells. By this contact, as by that of a magic wand, the cartilage-cells are metamorphosed, the chondro-

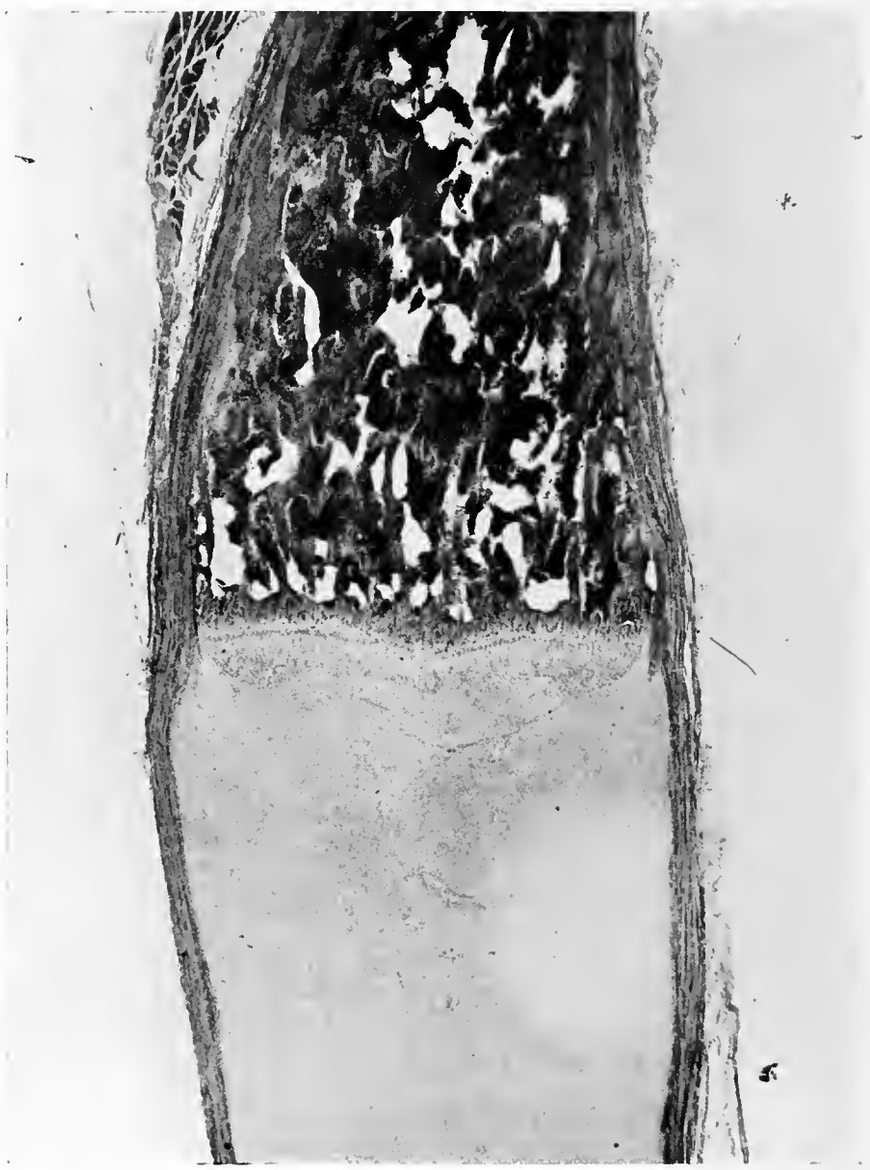


Fig. 12.

calcareous zone being seen in front of the vascular loops as the outpost of differentiation, and on either side of the loops the bone-cells are seen, formed either by neo- or by metaplasia.

Figs 14 and 15 show the growth-cartilage of the rib of a child which died at the same age, but from a lingering pneumonia. The "rachitic" thickening is visible in Fig. 14. The area of the enlarged cells—*i. e.* of the second stage of bone-growth—is widened out. The vascular loops

have penetrated it at different places. Fig. 15 represents some of these vessels. The cartilage-cells are larger than normal, and, close to the blood vessels, they show some modification; but no new bone-cells are formed. The magic power of the vessels (or rather of their contents) appears to be failing.

It is well known that pathologists have described as hyperplasia the thickening of the growth-cartilages of children said to be "rachitic."

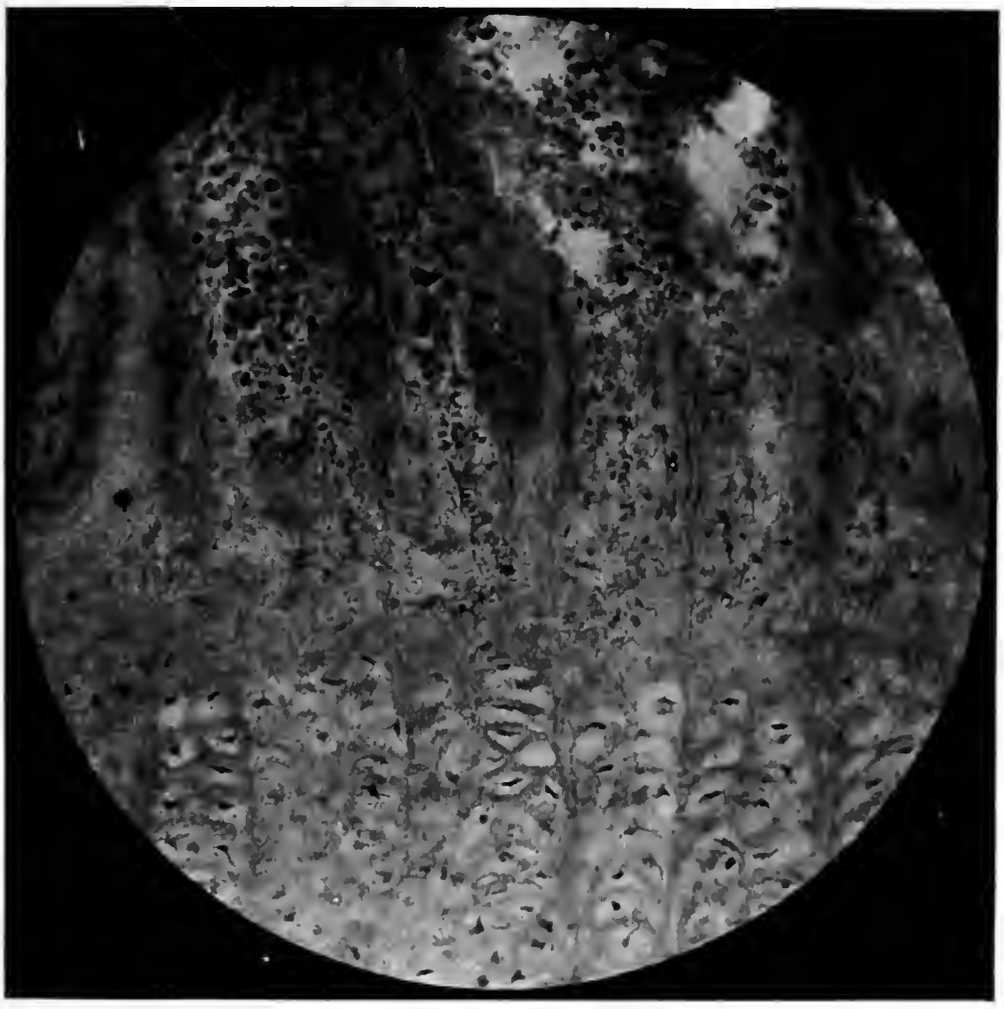


FIG. 13.

A strange form of hyperplasia, indeed, that leads to shortness of the bones, to a dwarfing of the whole individual! (cf. Figs. 2 and 3). If in a pottery a number of men have the modelling clay on one side and the modelled pots on the other, and if one man has more pots by his side than the others, the conclusion is not justified that this man has worked harder than the others. The man who had to carry the modelled pots to the oven may have been failing in his work. And all that we have been able to observe in our clinical and pathological study of "rachitis" leads us to conclude that the extra-retardation of differentiation of the cartilage-

cells is the cause of their being heaped up. These cells go on splitting up and enlarging; but the magic power of the vascular loops (or their contents) is exhausted.

In the growth-cartilages of "rachitic" children, as in the bones of the

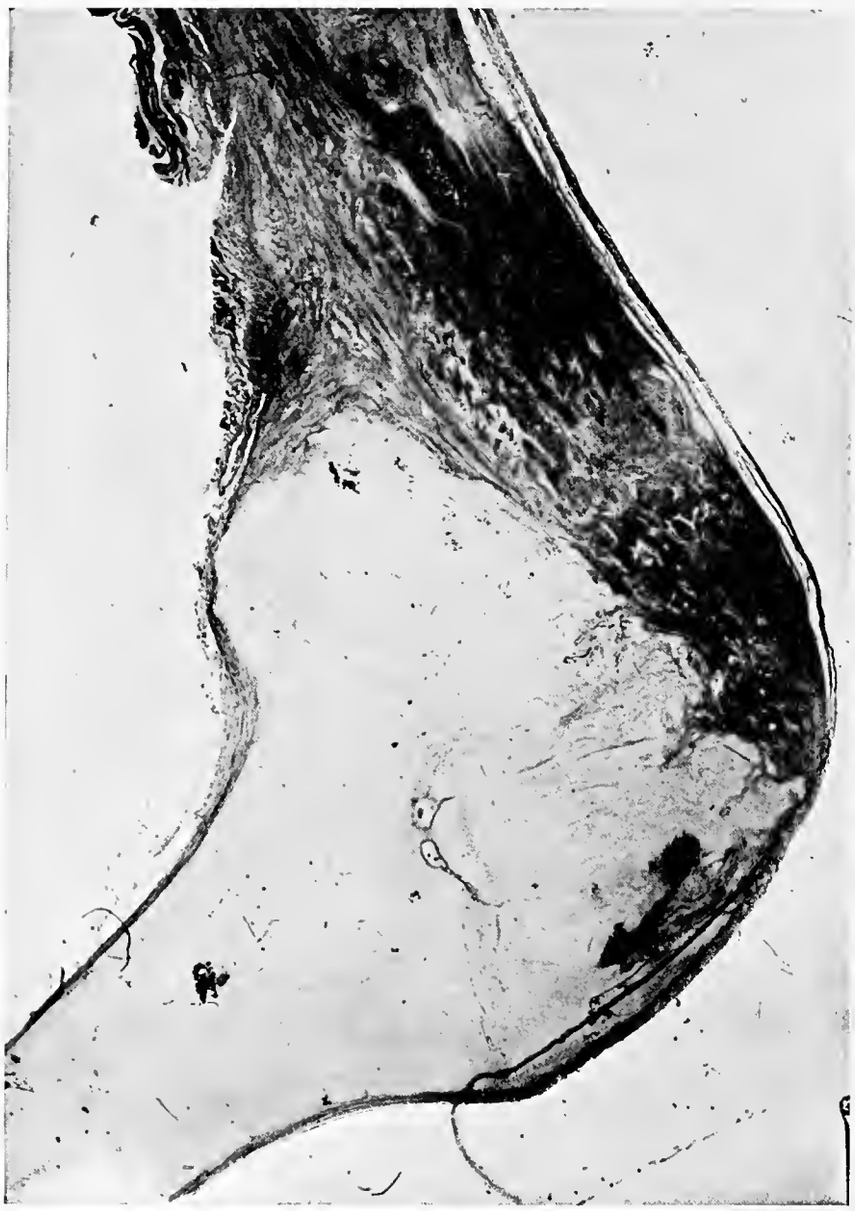


FIG. 14.

hand and of the knee which we have examined, *differentiation is retarded more than the two first stages of growth.*

The terms athrepsy and pædatrophy are, as we stated above, more severe forms of feebleness of growth than "rachitis." The names denote that there is no growth whatever, *i. e.* that the three stages of growth are all completely checked.

Now intermediately between "rachitis" and athrepsy there seems

to be a condition in which not only does cell-differentiation show extra-retardation, but both cell-differentiation and cell-enlargement are retarded more than is cell-division. At any rate Figs. 18 and 20 show a thickening of the area of cell-division which bulges on the surface of the rib, whilst the area of cell-enlargement shows no such bulging (in contrast with the "rachitic" specimen of Fig. 14). It therefore seems justifiable to assume that obnoxious agents which retard growth will retard cell-differentiation

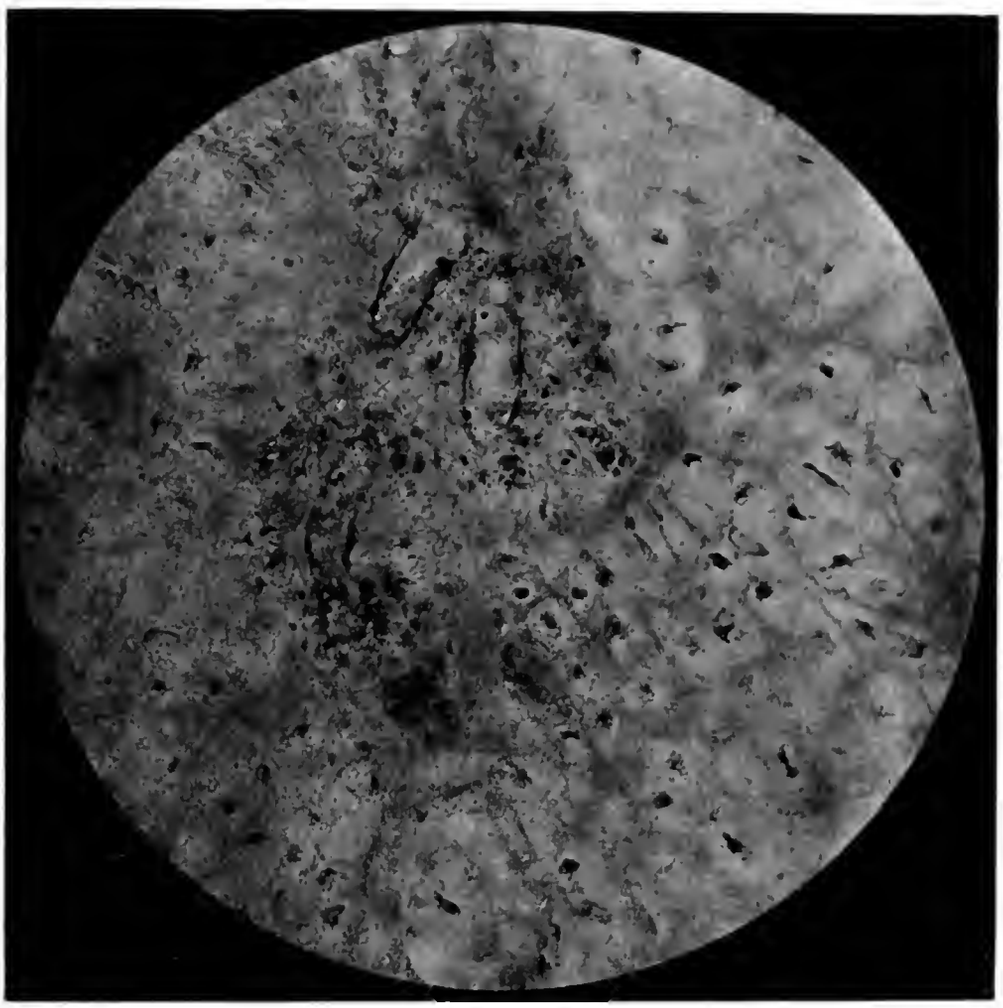


FIG. 15.

sooner and to a greater degree than cell-enlargement, and the latter sooner and more than cell-division. The specimens shown in Figs. 18 and 20 thus seem to represent conditions of more severe feebleness of growth than that which is termed "rachitis" (see Fig. 14). Be this as it may, it will become evident from what follows that not only the thickenings but all other phenomena in the growth-cartilages of diseased children accord with the view that obnoxious influences will retard or check in reversed order the three stages of growth: cell-division, cell-enlargement, and cell-differentiation.

Figs. 16 and 17 show the rib cartilage of a child which died at the age of one year and four months of scarlet fever and double pneumonia, *i. e.* of an acute disease. The growth-cartilage is hardly thickened. Cell-differentiation appears to be taking place: the zona chondro-calcarea

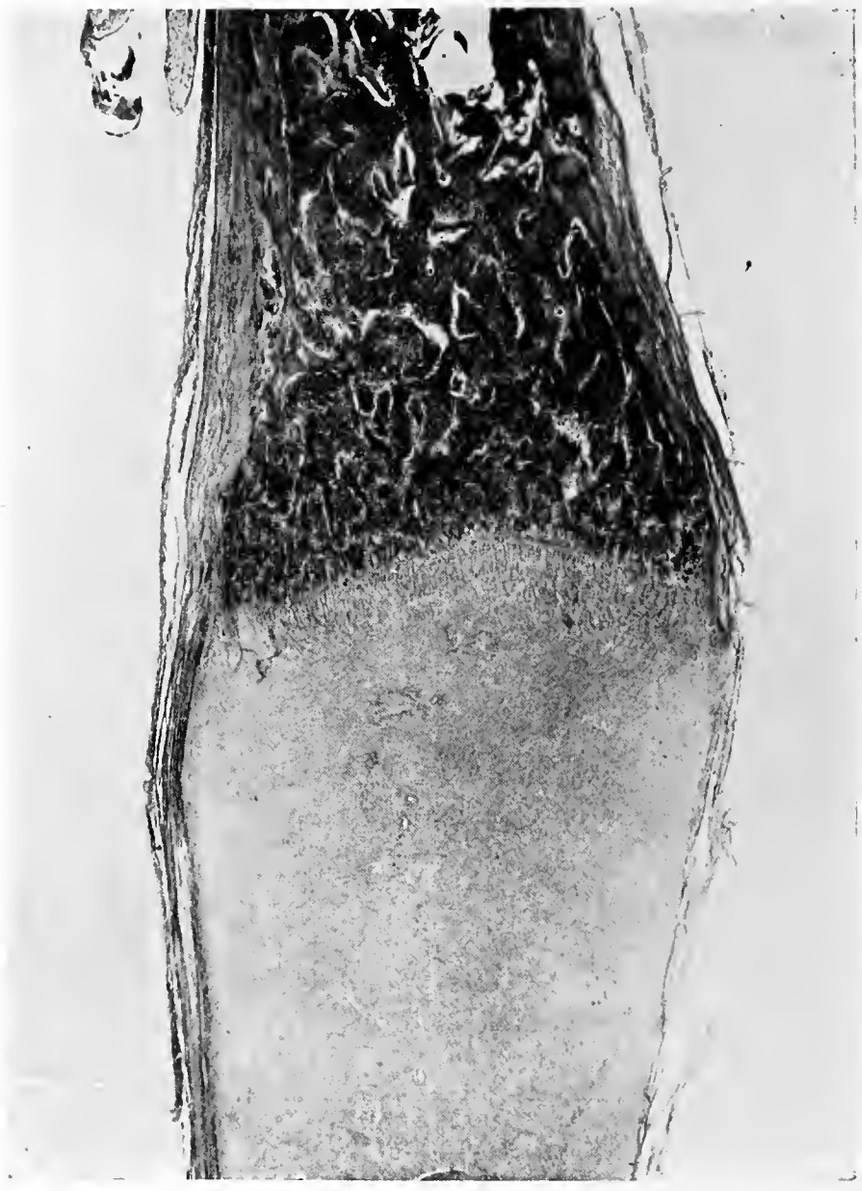


FIG. 16.

is present, bone-cells are to be found on either side of the vascular loops. But whilst in Fig. 13 cell-differentiation is visible down to the ends of the vascular loops, in Fig. 17 the signs of differentiation seem less distinct where the loops curve round. Hence here only slight retardation of cell-differentiation seems to be present. The condition, at any rate, is less serious than "rachitis."

Figs. 18 and 19, taken from a child which died at the age of one and a

half years of tuberculosis (of thoracic glands, lungs, pleurae, pericardium and peritoneum), cell-differentiation is more retarded than in the previous preparation: the zona chondro-calcarea is hardly, if at all, visible. The cartilage-cells on either side of the vascular loops do not seem to be all properly changed into bone-cells. The number of non-differentiated cartilage-cells is only slightly enlarged (slight lengthening of the columns of cartilage-cells or thickening of the growth-cartilage). There is bulging

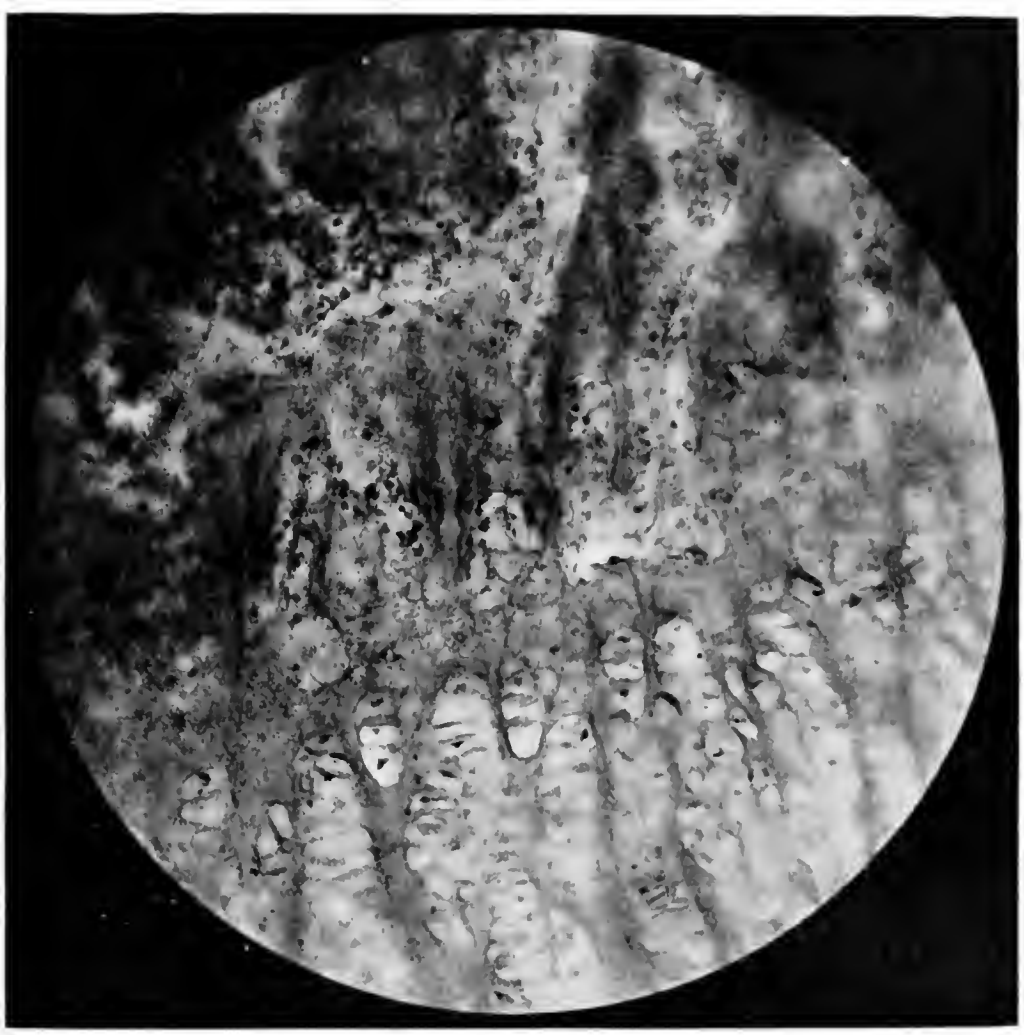


FIG. 17.

of the area of cell-division. Hence both cell-differentiation and cell-enlargement seem to have been more arrested than cell-division. The condition seems to constitute a more serious degree of feebleness of growth than is rachitis, and to approximate to athrepsy.

As soon as cell-differentiation is retarded, the diaphyseo-epiphyseal line shows irregularities which have attracted much attention from writers on the subject (see Figs. 14–19). Patches of cartilage may be found lying amidst ossified parts, just as reversely patches of bone may lie dispersed amidst cartilage. It might seem justifiable to conclude

from this fact that in "rachitic" growth-cartilages the changes are not only quantitative but also qualitative. And that is why we have made a special study of these irregularities.

Fig. 20 is the growth-cartilage of a child which died one year old, of

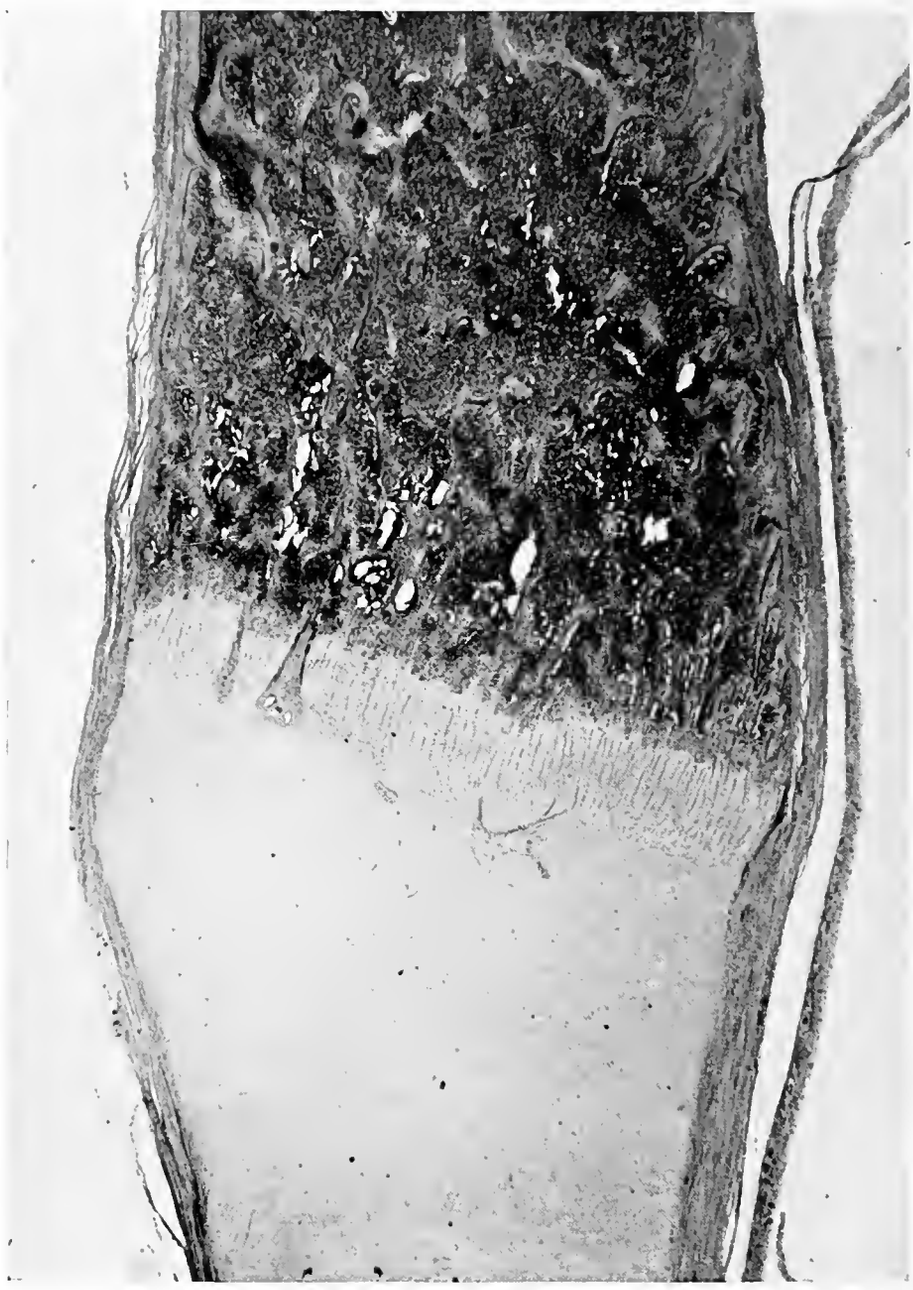


FIG. 18.

miliary tuberculosis. Here the columns of cartilage-cells are lengthened. The zona chondro-calcarea, the outpost of differentiation, is missing. Differentiation is retarded or checked altogether. The vascular loops, which in the normal condition are adapted each to its column of cartilage-cells, normally change the cartilage-cells into bone-cells (by neo- or metaplasia) while lengthening. And the bone-cells place themselves on

either side of each loop, so that it may continue its course toward new cartilage-cells. Though in Fig. 20 this differentiation is retarded or checked, the vascular loops continue to lengthen. They are seen to start from the bony end of the rib. But the cartilage-cells, instead of differentiating, remain such as they are and where they are. That must be the cause why the loops hit—*sit venia verbo*—against the cartilage-cells, get infolded and form balls, glomeruli (see Figs. 21 and 22). But

Fig. 19.

this at the same time is the cause of irregularities. The vessel-balls, enlarged as they are, are no longer adapted each to its column of cartilage-cells. They may meet and blend and thus separate patches of cartilage from the columns of cartilage-cells. This is seen in Fig. 23, where, moreover, a transverse strip of bone has been formed in front of the vessel balls, which have apparently fused. It is interesting to note how the normal condition may be re-established under those conditions. Fig. 24 represents vessels perforating such a transverse bone strip. The perforating vessels divide into several branches, each of which probably

seeks its own column of cartilage-cells for differentiation. That the perforation of the bone strips is achieved by means of large polynuclear cells, named "osteoclasts," is well known and is hardly of interest in the present connection.

The same irregularities are present in Figs. 25, 26 and 27, taken from

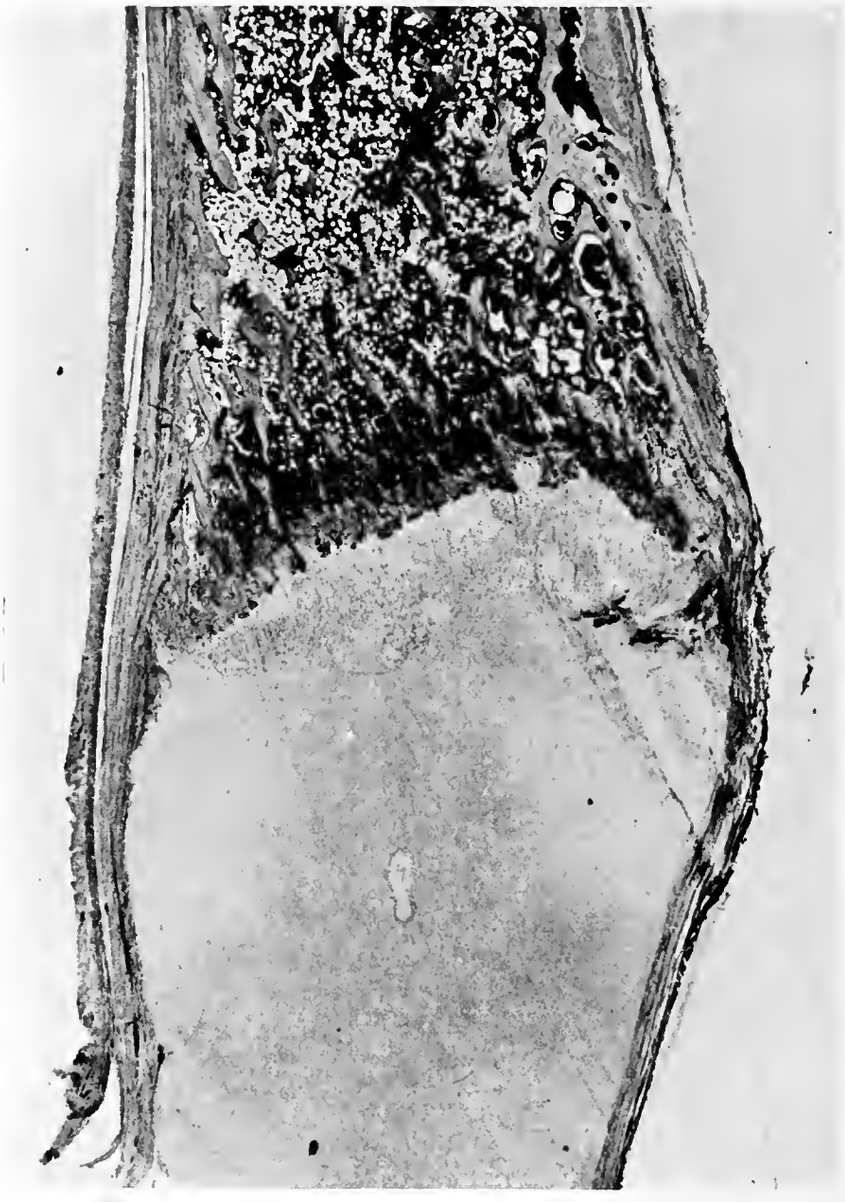


FIG. 20.

a child four-and-a-half years old, which died of tuberculosis with cavities of the lungs.

All in all the irregularities which the growth-cartilages present in children called "rachitic," as well as in conditions between rachitis and full arrest of growth, give us no right to assume that there are qualitative changes by the side of the quantitative changes we studied.

FIG. 21.

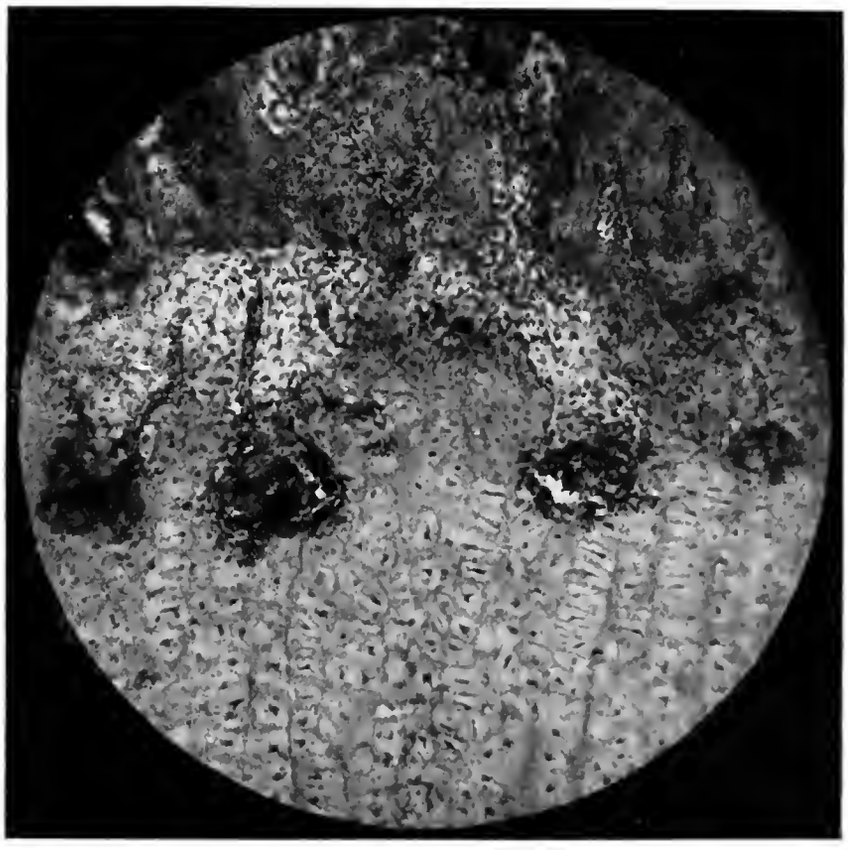


FIG. 22.

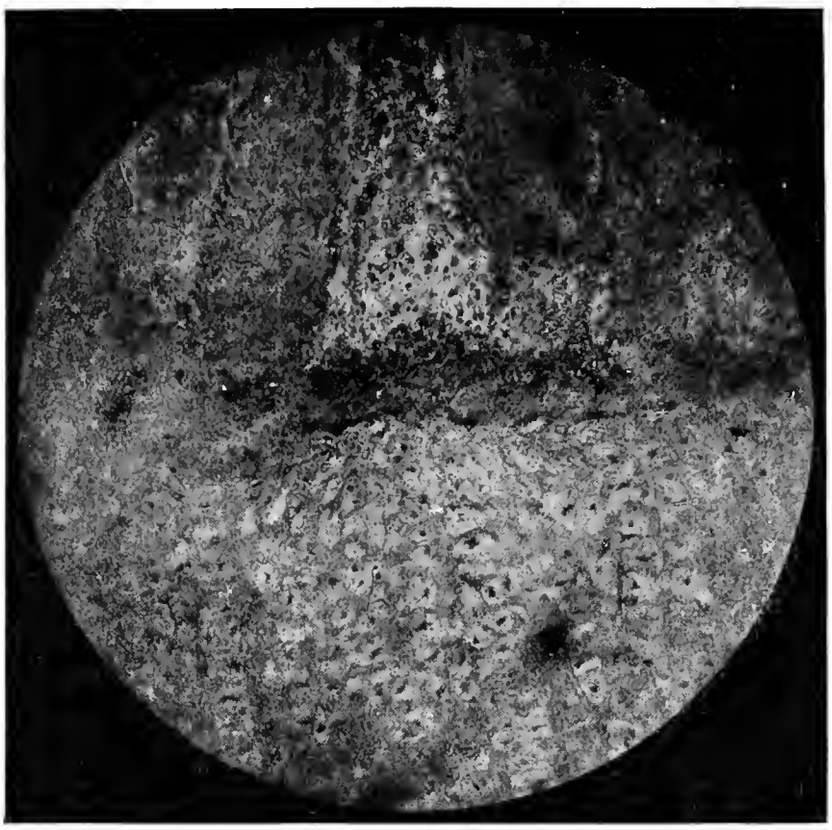


FIG. 23.

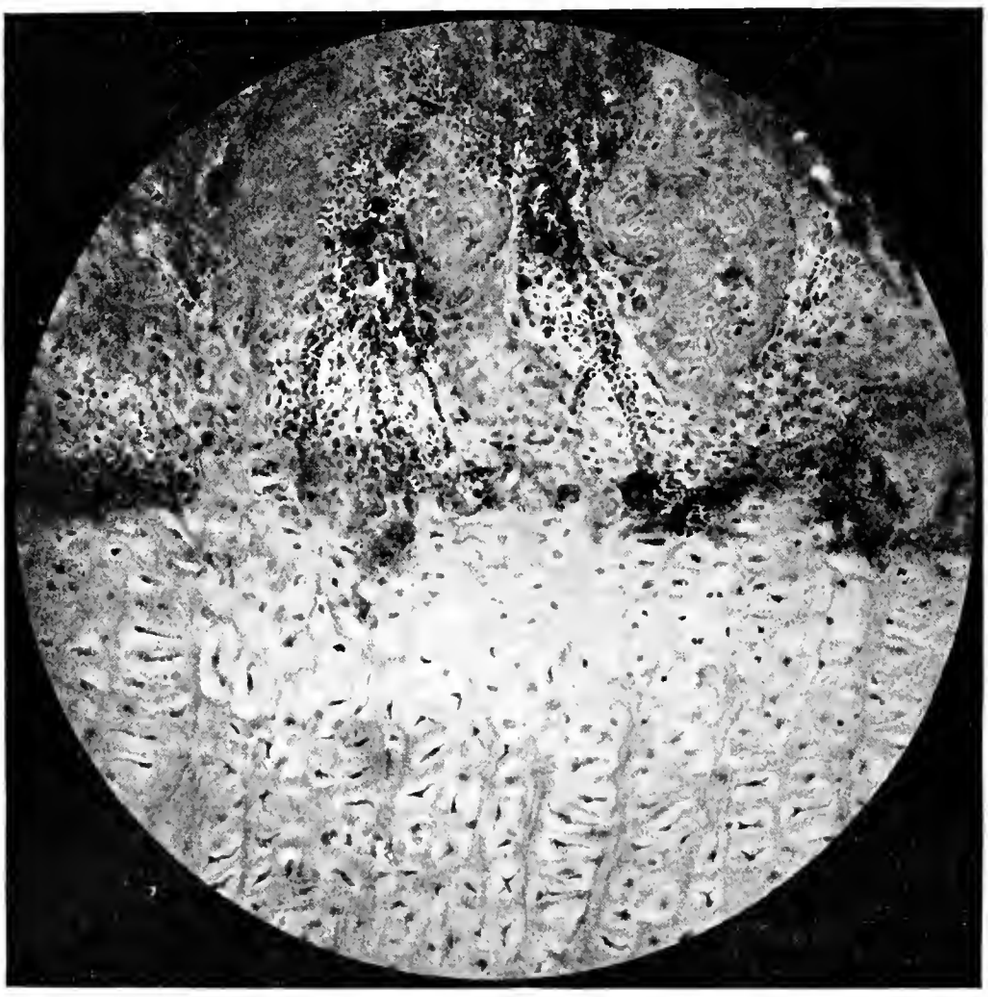


FIG. 24.

All the phenomena we have observed in the growth-cartilages of children which had died of some disease or another accord with the assumption that in feebleness of growth the three stages of growth, cell-division, enlargement, and differentiation, are retarded in reversed order; and that the lengthening

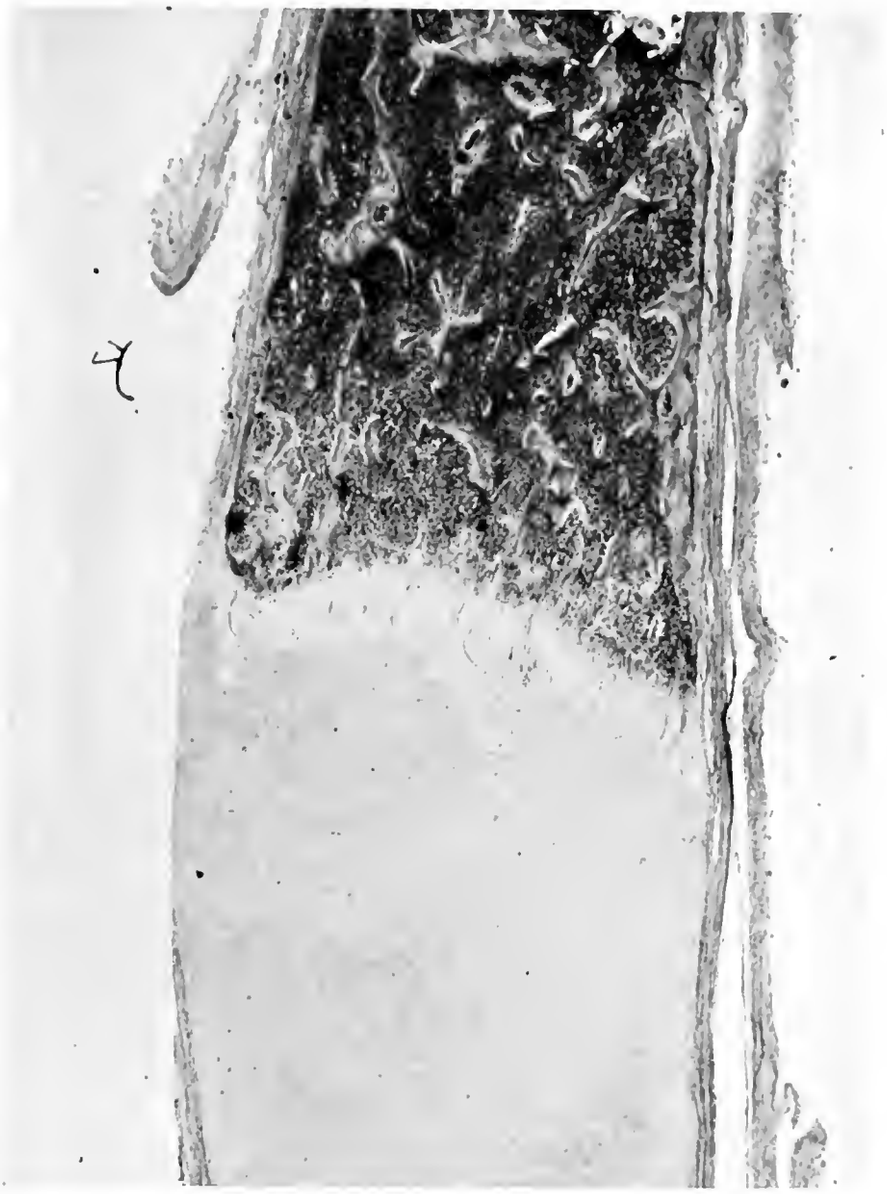


FIG. 25.

of the blood-vessels continues even after cell-differentiation has been checked altogether.

Hence in "rachitis" the cartilage-cells continue being formed, and being enlarged, whilst they are waiting for the magic agents which ought to transform them into (or to replace them by) bone-cells, for, although the blood-vessels appear to continue their growth, their contents have lost their differentiating power. The blood-vessels hit, so to speak,

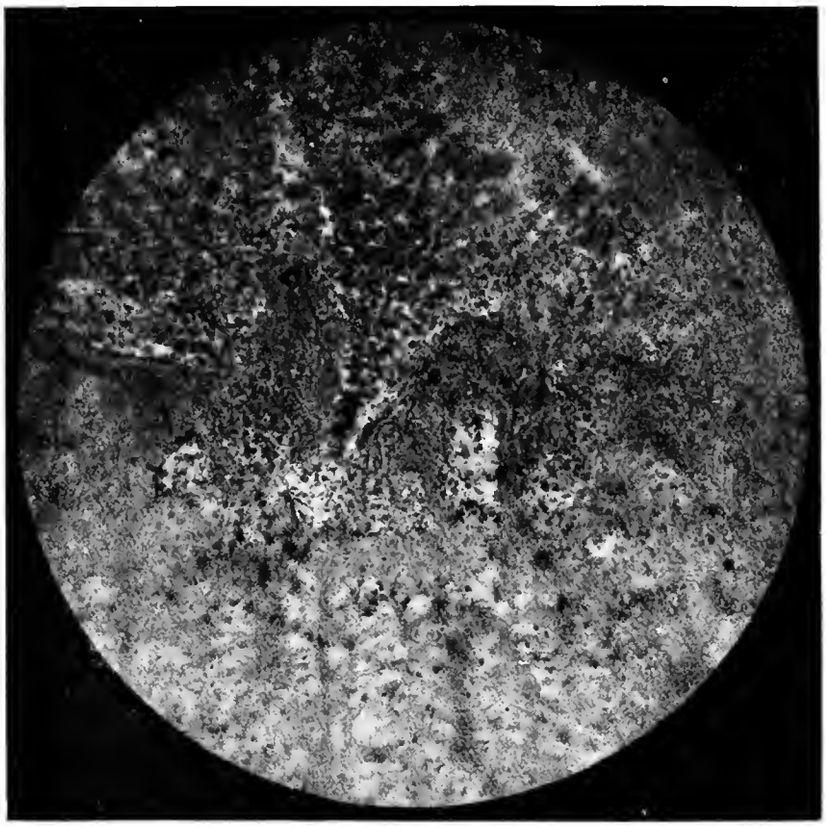


FIG. 26.

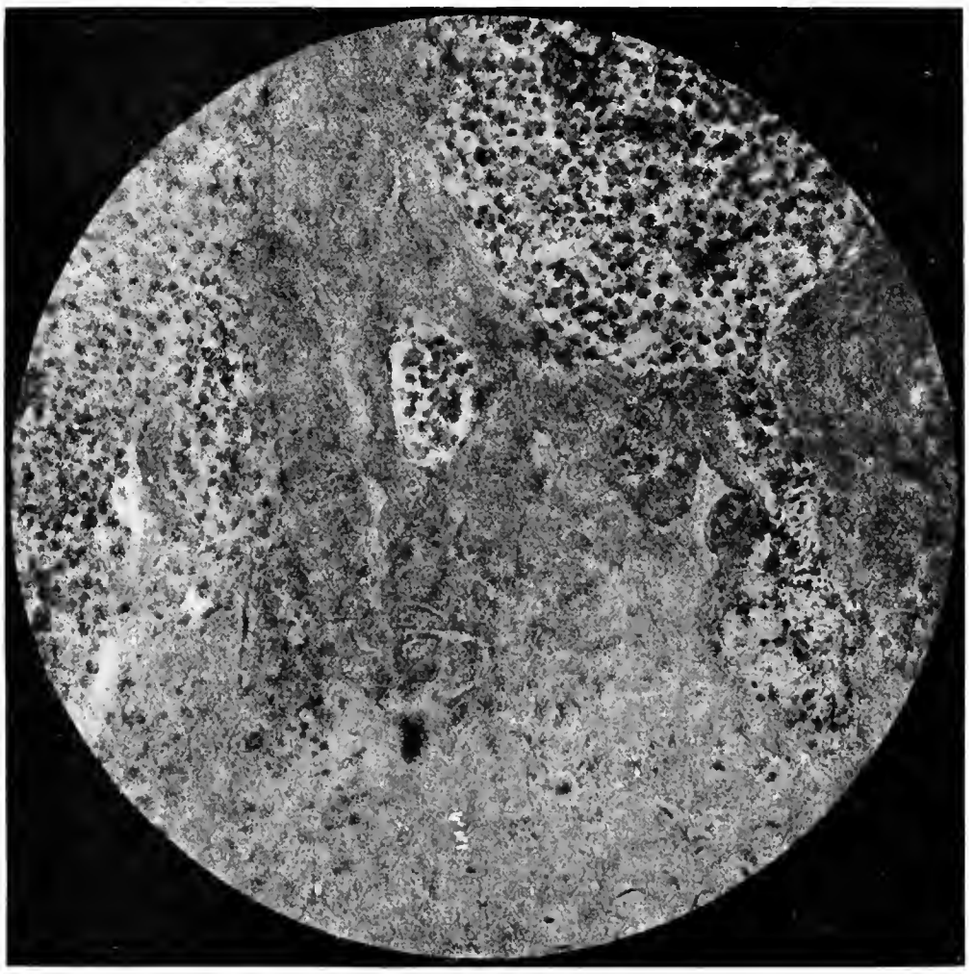


FIG. 27.

against the cartilage-cells, which, nevertheless, show no displacement and no change. The vessels are rolled up while growing, and thus give rise to the well-known irregularities in the growth-cartilage. And in less severe conditions, where differentiation is only retarded, not quite checked, so that no glomeruli are formed, yet irregularities must ensue from the fact that the cartilage-cells enlarge and disturb the mutual coaptation of cartilage columns and blood-vessels, inasmuch as the widening of the blood-vessels does not keep pace with the enlargement of the cartilage-cells.

III.—FEEBLENESS OF GROWTH CHARACTERIZED BY ENHANCED SENSIBILITY AND ENHANCED FATIGABILITY

In one of the preceding sections we have seen that the skeleton which evinces feebleness of growth, differs from the normal skeleton in its reaction to pressure. Where there is feebleness of growth in moderate degree we find a retardation of growth in the growth-cartilages near the knee—*i. e.* in those diaphyseo-epiphyseal discs which grow fastest—and particularly in the lateral part which is made to bear pressure surpassing the normal.

Where feebleness of growth appears in a severe degree there is a retardation of growth even where functional pressure does not exceed the normal (as in the metacarpal bones), while at the same time the difference of functional pressure in the different parts of any one of the growth-cartilages leads to a retardation on the side most exposed to pressure.

Hence the reaction to functional pressure of the skeleton in cases displaying feebleness of growth differs from the normal. In order to obtain a summary view of the different reactions, we will give a graphic representation of the phenomena of growth—of the normal skeleton as well as of that which is affected by feebleness of growth—in relation to functional pressure. By noting down functional pressure on the horizontal, and growth on the vertical axis, we obtain the following curves (see Fig. 28) :

No. I. For the normal skeleton ;

No. II. For the skeleton showing slight feebleness of growth (the skeleton which shows excess of height) ;

No. III. For the skeleton with severe feebleness of growth.

The continuous parts of these curves are based on clinical observations ; the dotted parts form their inevitable complement.

The point *n* represents normal pressure.

The clinical facts on which these curves are based, are the following :

For the normal skeleton, i. e. *for Curve I.*

(*a*) Persons with congenital luxation of both hips remain smaller than their brothers and sisters, unless reduction be effected. Hence diminution of functional pressure causes retardation of growth. This is represented by the non-interrupted part of Curve I., which is traced to the left of the vertical arising from *n*.

(*b*) The curved legs of normal children that begin to walk have a well-known tendency to grow straight. The straightness of the lower extremities of normal adults is the evidence for it. There is no doubt

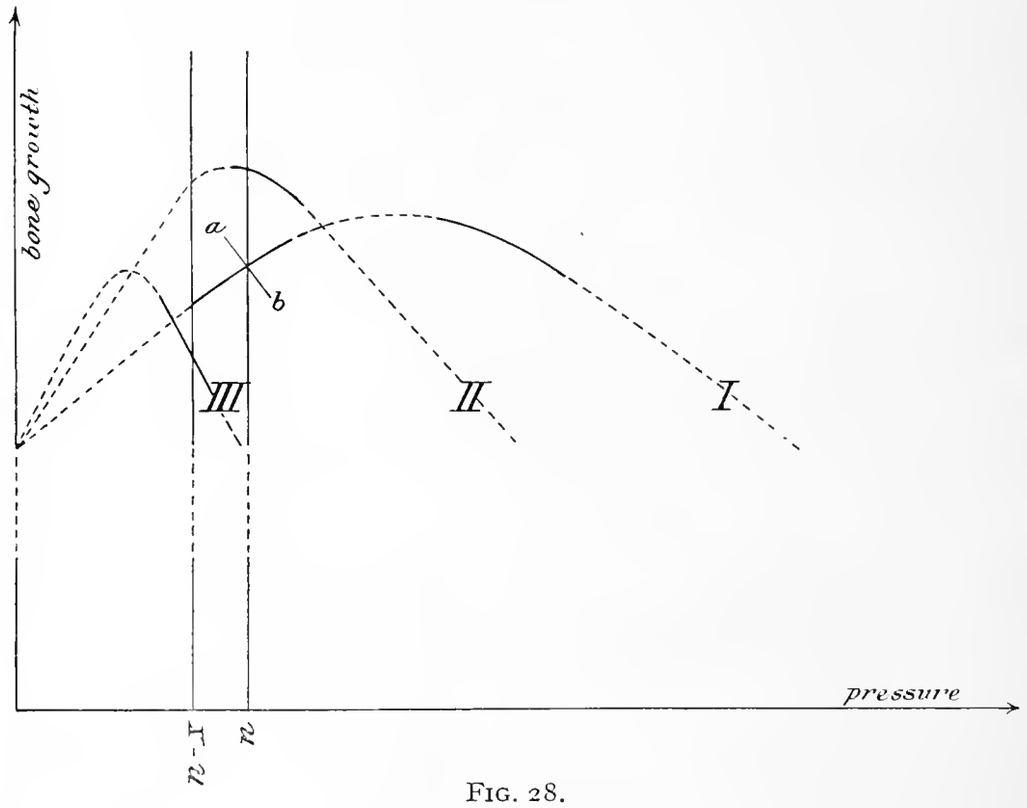


FIG. 28.

but that the concave side of these little legs is made to bear more pressure than is the convex side, so that the part of the bone in which pressure exceeds the normal, develops a more rapid growth. This power of the normal bone to accelerate growth wheresoever functional pressure exceeds the normal, may be termed the *reserve power of growth.* It is represented in the continuous part of Curve I., to the right of the vertical which arises from *n*.

In case the leg, after having grown straight, should continue to develop more growth on the same side, the genu varum which was present at the onset, would change into genu valgum. But then the lateral side would be made to bear more pressure and would accelerate its growth, and vice-versa. Hence the reserve power of growth does not only cause

the curved legs to grow straight, but also to remain straight during normal growth.

(*c*) Physiology teaches us that the increase of a stimulus does not cause unlimited increase of the biological reaction to it. Far from being proportional to functional pressure, as Wolff's "law" proclaims, growth reaches a maximum after pressure has exceeded the normal by a certain amount. After that the curve passes into an *indifferent stage*, and descends even when the stimulus continues increasing. And inasmuch as the pressure of the shoes of Chinese women may be compared with functional pressure, the smallness of the bones of these compressed feet may be taken as an example which is represented in Curve I. by the continuous descending part.

For the skeleton with slight feebleness of growth, i. e. *Curve II.*

It is generally known that young persons who grow to excessive height, have an enhanced tendency to develop knock-knees. The weak feet they regularly have—as we have seen—though causing an increase of functional pressure in the lateral half of the growth-cartilages near the knees, do not always cause knock-knees. But, as soon as these unfortunate individuals have to walk or stand much, and especially if they are made to carry heavy weights, knock-knees do not fail to appear. This is represented by the continuous part of Curve II. And this continuous part crosses the vertical, arising in n, a little higher than Curve I. in order to indicate that in response to normal pressure (the body-weight of those who have out-grown their strength, does not necessarily differ from the normal) growth surpasses the normal.

For the skeleton with severe feebleness of growth, i. e. *for Curve III.*

In severe feebleness of growth the muscles are exceedingly flaccid, and the child, lighter than normal though it be, walks too late and too little. Hence functional pressure in it remains below the normal. Let us call it $n - x$. In the skiagram of the "rachitic" metacarpals we have observed that this pressure $n - x$, even though below the normal, retards normal growth. This is represented in Fig. 28 by the fact that Curve III. crosses the vertical, arising from $n - x$, in a point lower than that in which Curve I. crosses the vertical arising from n.

In previous sections we have seen moreover that each difference of pressure in different parts of the same growth-cartilage gives rise to a difference of growth. This is represented by a rapidly descending direction of the continuous part of Curve III.

Though we have not brought forward any clinical facts to prove that

the Curves II. and III. have an ascending as well as a descending part, there is no doubt but they have it. And it is evident that the continuous parts of the three curves have to be completed in a way resembling essentially that of Fig. 28.

It must be emphasized that these curves convey only a rough approximation of the real relations; that they are far from being a mathematical representation of the facts. We are moreover aware that we have left out of consideration the biochemical stimuli for bone-growth (*e. g.* from the pituitary body). However, since these afford a stimulus for bone-growth as well as do the mechanical stresses of function, it is probable that the curves representing their action largely follow the same direction and *ceteris paribus* show the same changes, and that from the intermixture of mechanical and biochemical stimuli no essential difference ensues. If for all that we may not claim that our curves should be considered to represent established scientific fact, yet they may be accepted as illustrating a proposed theory on the phenomena of feebleness of growth with regard to functional pressure. If we are right in accepting them as such, we may conclude from them that in feebleness of growth the growth-curves have a more rapid ascent and descent than in the normal condition. *The sensibility of the skeletal cells is enhanced.* Moreover they start their descent in response to less pressure than in the normal conditions. *The fatigability of the skeletal cells is enhanced.* The curve descends in response to a pressure which is less, in direct proportion to the degree of feebleness of growth. Finally, Fig. 28 shows that in the cases of feebleness of growth which clinically present themselves most frequently—*i. e.* in slight cases, in which functional pressure comes near to the normal—enhanced sensibility places itself in the foreground (growth rises above the normal), whereas fatigability is characteristic of feebleness of growth in severe degrees (growth lags behind).

It stands to reason that between the three curves all transitions occur in the living body. The line *ab*, e. g. (see Fig. 28), is part of a curve between II. and III., between slight and severe feebleness of growth. It represents what the so-called Hueter-Volkmann's "pressure theory" expresses, according to which growth is retarded ("vermindert"), whenever pressure surpasses the normal, and that growth is accelerated ("begünstigt"), whenever pressure is diminished. Hueter-Volkmann's "theory" thus appears to be far from laying down a rule for all cases of skeletal growth. It bears reference only to a very special condition. And, if the words "vermindert" and "begünstigt" are used with regard to normal growth, the line *ab* is the only one to which Hueter-Volkmann's "theory" bears reference.

The curves of Fig. 28 are not only of theoretical interest, but also of

practical importance. They suggest that in genu valgum every diminution of functional pressure brings the chance of improvement nearer. If, for instance, in an individual growing according to Curve II., a knock-knee has developed under a pressure $= n$ on the medial part of the growth-cartilage, and a pressure $= n - x$ on the lateral part, cure will be effected, as soon as we succeed in diminishing the pressure to $n - x$ and n respectively. The general rule follows from it that in knock-knees fatigue has to be avoided in walking as well as fat in nutrition (increasing the body-weight).

In the preceding section we have seen that the third stage of growth, that of cell-differentiation, is retarded earlier than the two first stages. Differentiation thus appears as a more elaborate process of growth than the two first stages. It appears to be affected more seriously—so to speak—by a more severe degree of feebleness of growth than the two first stages. If it be permitted to apply the curves which we have just constructed for the various degrees of feebleness of growth, to the three stages of growth, we may imagine that in rachitis cell-differentiation may behave according to Curve III., whilst the second growth stage, cell-enlargement, follows Curve II. Hence the possibility must be considered that in certain cases of rachitis the thickening of the growth-cartilage results not only from a retardation of cell-differentiation, but also from an acceleration of cellular enlargement. For obvious reasons this is more probable for moderate—almost slight—degrees of feebleness of growth rather than for the severe cases.

And the same consideration may hold good for cell-division as with regard to cell-enlargement, so that possibly the former may follow a curve coming near to II., whilst the latter follows one more like III.

SYNOPSIS OF FEEBLENESS OF GROWTH

Summing up, feebleness of growth may be caused by any injurious agent acting on a growing body.

It is proportional to the intensity of the nocive agent.

It is proportional to the rapidity of growth :

(*a*) Of the *individual*, so that severe degrees of feebleness of growth belong to the first years of life;

(*b*) Of the *parts*, so that first the musculature suffers, next also the skeleton. In the skeleton it is first the growth-cartilages which are affected, and of these again first those which grow most rapidly.

Feebleness of growth seems to be characterized by enhanced sensibility

and enhanced fatigability of the skeletal cells. In slight degrees the enhanced sensibility of the growth-cartilages determines the clinical picture, so that the height of the individual exceeds the normal. In severe cases enhanced fatigability dominates the clinical aspect. A retardation of growth results : the body-height remains behind the normal. At the same time the enhanced sensibility to pressure causes deformities, a difference of growth resulting from each difference of pressure.

In feebleness of growth the three stages—cell-division, enlargement and differentiation—seem to be affected in reversed order. At all events the third stage is retarded sooner and to a greater degree than the second and first. So it appears as though it were the result of a severer degree of feebleness of growth than the two first stages. A heaping up of cartilage-cells results. The vascular loops continue to lengthen even after their contents have lost their power of stimulating the cartilage-cells to differentiation. Irregularities in vascularization and ossification result.

The possibility must be taken into consideration that in slight cases of feebleness of growth cell-division and enlargement surpass normal growth, even when differentiation is retarded; that in other words, while cell-differentiation is behaving according to Curve III., cell-enlargement and cell-division behave according to curves nearer to II. And similarly for severer cases the possibility must be considered that cell-differentiation and cell-enlargement may go on according to curves coming near III., cell-division according to a curve coming nearer II.

CONSIDERATIONS AS TO FEEBLENESS OF GROWTH AS AFFECTING ORGANS OTHER THAN THE LOCOMOTOR APPARATUS

The phenomena of feebleness of growth which we have described are localized in the locomotor apparatus. They are the symptoms that are of vital interest to the orthopædist. We might, therefore, have restricted ourselves to the description of the above conditions. But it seems useful also to insist on their significance for the physician. For in the first place the physician will have to advise as to the prophylaxis of these conditions; in the second place he will have to ascertain to what degree other organs partake of feebleness of growth. He will have to study the susceptibility to disease in feebleness of growth, and the biological reactions generally. We have reason to assume that every individual showing feebleness of growth (of the locomotor apparatus) has undergone changes of other organs; that, therefore, the symptoms of feebleness of growth may serve not only as a basis for estimating bodily strength, but also that they may afford suggestions as to the susceptibility to

diseases, and as to the reaction of the organs generally. And though we have not had an opportunity of studying the changes of internal organs in cases of feebleness of growth, we beg leave to present a few considerations that may be useful to those who are willing to undertake the task indicated.

TABLE I

INDICATING THE PERCENTAGE WHICH THE PRINCIPAL ORGANS NORMALLY CONTRIBUTE TO THE BODY-WEIGHT

Percentage of the Body-weight.

	In the newborn child.	In the adult.
Of Muscles	25·05	43·40
Skeleton	13·7	17·48
Skin and subcutaneous tissue	19·73	17·77
Brain	12·29	2·16
Liver	4·57	2·75
Stomach and intestine	2·1	2·00
Lungs	1·75	1·50
Heart	0·76	0·46
Kidneys	0·75	0·46
Spleen	0·34	0·25
Thymus	0·26	0·04
Eyes	0·24	0·02
Suprarenal glands	0·23	0·01
Salivary glands	0·21	0·12
Spinal cord (without membrane)	0·18	0·06
Thyroid body	0·16	0·05
Pancreas	0·11	0·15
Ovaries	0·026	0·012
Total	81·93 per cent.	88·43 per cent.

(a) *Of the skin and mucous membranes.*

If we study Table I., which we derive from Vierordt [1] by arranging the organs in the order of their weight, it is evident that after the muscles and the skeleton, the skin and subcutaneous tissues constitute the highest percentage of the body-weight.

What share each of these tissues contributes to this percentage is unknown to us. Nor do we know what percentage the epithelium covering the external and internal surface of the body—that of skin, intestine, bronchi, lungs—contributes to the body-weight. But this much we know, that in young children with feebleness of growth the subcutaneous fat as well as the epithelium reveal to us symptoms of their participation. Young children with feebleness of growth are generally characterized by

[1] Vierordt, *Daten und Tabellen*, 1906, p. 44.

their thinness. And where the nocive agents have been in operation before birth, the children are born thin.

As regards the epithelium the type of knock-kneed children, as well as the "rachitic," often have a tendency to inflammations of the epithelium of the skin (eczema), of the intestine (enteritis), of the bronchi (bronchitis), and of the lungs (pneumonia). This condition in our days has been called "exudative diathesis," after Czerny. Fatty food is hardly tolerated and gives rise to eruptions (urticaria). We will not for the moment discuss the question whether this condition is to be considered as feebleness (of growth) of the epithelium or rather as a true diathesis, *i. e.* a qualitative change of the normal condition. For the solution of this problem a comparison of children, suffering from this diathesis, with their brothers and sisters with regard to the nocive agents to which they have severally been subjected, will be necessary. And inasmuch as the symptoms of "exudative diathesis" will reveal a parallelism with feebleness of growth and follow its principles, they will thus show an indisputable relation to it.

(b) *Of the nervous system.*

After the skin and subcutaneous fat the brain of the newborn child furnishes the greatest contribution towards the body-weight. Later on the rate of growth of the brain normally slows down. The sharp intelligence of persons even with severe feebleness of growth—for instance of the humpbacked—pleads in favour of the assumption that in feebleness of growth the brain is not subjected to the law of the vulnerability of fast-growing cells in the same degree as the muscles and the skeleton. Therefore the possibility must be considered that besides the principles which we have tried to establish, there are others that may enter into action in determining the degree of retardation of growth of organs in cases where nocive agents affect the growing body. It is said that in animals that are starved, the nerve-cells and the sexual glands retain their condition after the other organs have wasted.[1] By analogy the possibility must be admitted that the human body also, in case of nocive agents threatening its existence and arresting its growth, has a tendency to preserve those organs which are of the greatest physiological importance, such as the brain and the sexual glands. Accurate research will be necessary to determine in what measure the law of the vulnerability of fast-growing cells, and to what extent *some rule of the preservation of organs indispensable for the maintenance of the individual and the species* (as the controlling and the reproductive apparatus), determine the effect of a nocive agent on the growing organs in question. However, it seems

[1] H. Driesch, *Gifford-Vorlesungen*, 1909, Bd. II. p. 203.

reasonable to believe that the development of the brain will be better accomplished in the absence of nocive agents than when they are present. And quite certain it is that feebleness of growth changes its reaction. The irritability of the humpbacked, for example, is proverbial. In other words, the nervous system of persons with severe feebleness of growth reacts according to a curve with steeper ascent and descent than in the normal subject (cf. Fig. 28). And we have reason to assume that this is the case—though in a less degree—in persons with slight feebleness of growth with regard to the cerebro-spinal as well as to the sympathetic system. We are convinced that the nervous system of these persons has an even greater tendency than in the normal subject toward enhanced irritability of the nervous system generally, of the vagus in men, and of the sympathetic in women specially—a difference in sex to which my former chief and esteemed friend, Prof. Nolen, has directed attention. In severer cases an enhanced tendency toward asthenia may be considered probable. Moreover, it is probable that in all these cases not only are the epithelium and serous membranes more sensitive to the nocive agents than normally, but also the parts of the joints (arthritis) and the internal organs (lithemia).

Be this as it may, in cases of enhanced irritability of the vagus and sympathetic, asthenia, arthritis, lithemia and many other conditions physicians have to deal with, attention will have to be paid to the presence or absence of symptoms of feebleness of growth. And it will be necessary to compare the subjects with their brothers and sisters with regard to the action of nocive agents, in order to determine the share these nocivities may have had in the development of the symptoms.

(c) *Of the sexual glands.*

As regards the sexual glands it must be observed that those of women contribute only a small share to the general body-weight. They are at the bottom of Table I. Their weight therefore suggests a late participation in any feebleness of growth that may have been operative in childhood, even apart from any natural tendency to the preservation of indispensable organs. Of course this does not hold good for the ripening ovum in the adolescent and adult female, which, though small, grows beyond the proportions existing previously, and is therefore more susceptible to injury.

In the adult male the active cell-division renders the sexual glands extremely vulnerable, as has been shown by the action of X-rays upon their spermatogenic function. That is why the poisoning of the father—*e. g.* with tobacco—before procreation seems not to be without importance for the normal development of the child. In fact the enormous number of persons in northern countries whose excess of body-height,

round back, flat feet, and blue, moist hands show that they have outgrown their strength—briefly : of persons with slight feebleness of growth —has suggested to us the hypothesis that the tobacco, often abundantly indulged in by the father, might sometimes be one of its causes. And the comparison of children generated while the habit of smoking is indulged in with others generated by the same parents in its absence, may enable us either to confirm or refute this hypothesis.

(d) *Of the police (adenoid) tissue.*

To one more symptom attention must be directed, viz. to the fact that in children with moderate and severe feebleness of growth in the families we have observed, there is a tendency to keep the mouth open. The police (adenoid) tissue of these children shows signs of hypertrophy in the tonsils as well as in the lymphatic glands of the axillæ and the inguinal folds. This condition used often to be termed " scrophulosis."

We will not now discuss the question in what measure this hypertrophy of the police tissue is to be considered as a sign of feebleness of growth or as a qualitative change, a specific diathesis. We will restrict ourselves to the observation that inasmuch as this hypertrophy shows a parallelism with the symptoms of feebleness of growth, its relation to this condition cannot be denied. At all events it may be considered as adequate a measure of the weakened body as is the preservation of the nervous cells in the starving animal.

Be this as it may, certain it is that the terms used by clinicians of our days, some of which we have mentioned in our study, as " *rachitis,*" " *exudative diathesis,*" *irritability, asthenia, arthritism, lithemia,* have the merit only of bringing together a group of symptoms—neither more nor less. They give no idea as to the nature of these symptoms nor of their relation to the normal condition. The same thing holds good for " *lymphatism* " (the hypertrophic as well as the atrophic form), *status thymico-lymphaticus, status thymicus, hypoplastic constitution, infantilism, susceptibility to infections,* and the terms *crasis* and *dyscrasia.* Of other conditions, *e. g.* chlorosis and Little's disease, it may be said that they will never be understood unless the law of the vulnerability of fast-growing cell-groups be applied. And he who wishes to trace the nature and the cause of these various conditions, will have to start his research by comparing those individuals who are affected by them with their brothers and sisters with special regard to the nocivities to which they have been subjected. And only those who can then uphold the view that a growing body may be subjected to any nocive agent without its growth being affected, will be able to discard the conception of feebleness of growth and its principles here presented.

PART II

CONGENITAL DWARFISM

(With special reference to Dysostosis Cleido-cranialis)

INTRODUCTION TO THE SECOND PART

The phenomena of congenital dwarfism with which this second part deals, constitute a special case of those of feebleness of growth which were discussed in the first part. In the first part all possible injurious agents were taken into consideration, in this part only a single nocive agent will be considered, viz. compression—and through it ischæmia—of flexible parts of the embryo and fœtus. In the first part, moreover, the nocive agent always acted on the whole of the growing body. In this part it often acts locally (see Postcript, last paragraph). In the first part, finally, the slight degree of feebleness of growth, which is characterized by excessive growth, was treated as well as the severe degree. In this part, however, the slight degree will not be met with, or—if at all—under such modified circumstances that the two cannot be identified. Hence only the severe degree of feebleness of growth, *i. e.* dwarfism or death, will be met with in this part.

The two principles, the establishment of which forms the aim of this book, will therefore manifest themselves in this part in the following way :

(1) Compression of flexible parts of the embryo diminishes or arrests blood-supply.

(2) Diminished or arrested blood-supply dwarfs or kills the affected parts.

(3) Growth-stunting is effected first and most in those parts which grow fastest. (Law of the vulnerability of fast-growing cell-groups.)

For the right understanding of the purport of this, it should be noted that the rapidity of growth of the embryo goes on decreasing from the first month, and probably even from the first days, after fecundation. The length of the fœtus each month increases from 1 cm. at the end of the first month to 4, 9, 16, 25, 30, 35, 40 and 45, amounting to 50 cm. at birth. Hence from the second month upwards it is 4, $2\frac{1}{4}$, $1\frac{7}{9}$, $1\frac{9}{16}$, $1\frac{1}{5}$, $1\frac{1}{6}$, $1\frac{1}{7}$, $1\frac{1}{8}$ and $1\frac{1}{9}$ times the length of the previous month—which in that time means a decrease of the rapidity of growth, *i. e.* of cell-division, and consequently a decrease of vulnerability. Moreover, in fœtal—far more than in post-natal—life the development of the different parts varies

in rapidity. The parts of the growing body constantly change their proportions. Some part will suddenly start rapid development, thus outgrowing previous proportions, while later on the power of growth is concentrated on quite a different part. For example the head, not present at the end of the second week, grows to be about half the size of the whole body in the third week. So this is a time of greater vulnerability to the head than to the rest of the body. Hence, as the rapidity of growth of the embryo as a whole determines its excessive vulnerability in the first few weeks, so the fact that the head outgrows its previous proportions in the third week, determines the extra-vulnerability of that part in this period.

Since in this second part pressure is made responsible for the dwarf phenomena, only such cases of congenital dwarfism will be discussed as are attended by mechanical malformations. We know a series of such conditions, *i. e.* conditions characterized by phenomena of dwarfism, or even absence of parts, which are regularly attended by mechanical malformations. And each of these mechanical malformations will prove to be the characteristic attendant of certain dwarf phenomena. Such conditions composed of dwarf phenomena and mechanical malformations will in the following be termed *composite* (*congenital*) *deformities*.

The mechanical malformations of the composite deformities have hitherto been little studied. They have partly been overlooked, apparently overshadowed by the much more impressing dwarf symptoms. Yet the mechanical malformations are of primary importance, since they give valuable hints both as to the time and the manner of the origin of the composite (congenital) deformities. They, indeed, give evidence favouring the assumption that smallness of the amnion is to be made responsible for the pressure. And the remarkable facts present themselves that :

(1) The dwarfism by which each of the mechanical malformations is attended, is located in those parts which were growing fastest—*i. e.* which were outgrowing previous proportions—at the time of the origin of the mechanical malformation.

(2) The composite (congenital) deformities constitute a chronological series.

The following composite congenital deformities may be alleged as illustrations. They will be discussed only briefly forasmuch as they have been dealt with elsewhere—in which case for further details reference will be made to the corresponding literature. Only Dysostosis Cleidocranialis, which has not yet been considered in the manner indicated in the above, will be treated more elaborately.

ANENCEPHALY [1]

This condition is characterized by growth-stunting of brain and skull. It is regularly attended by a high dorsal kyphosis, whilst the cranial and the caudal ends of the trunk are turned backward. In short, the phenomena of growth-stunting are attended by a "wrinkling" of the body-axis. This wrinkling must have been brought about at a time when the spine is still flexible, sclerob!astematous, *i. e.* before the fifth week. In the third week—as is well known—the embryo accomplishes its physiological infolding. After this physiological infolding a compression by the amnion would only lead to an accentuation of the backward curve of the embryonic axis. Hence the pressure which produces the wrinkling of the embryonic axis in Anencephaly, must have acted before the beginning of the third week, viz. at a time when the amnion is in contact only with the posterior surface of the embryo. In consequence of the fact that the length-growth of the embryo outdoes its increase in breadth, its head and its tail are caught in a kind of hood, when the growth of the amnion does not keep pace with that of the embryo; and its membranous body-axis will develop folds or wrinkles, such as are constant in Anencephaly. Thus the mechanical malformation in Anencephaly demands for its origin the second or the beginning of the third week of embryonic life.

The head of the embryo is not yet present in the second week. It starts its development in the third week, at the end of which its size amounts to about half of the rest of the body. The rapidity of its growth in this period determines its vulnerability to be much greater than that of the tail-end. Therefore, though exposed to the same pressure, the head-end may be dwarfed or killed whilst the tail-end continues its growth.

Thus Anencephaly demands for the origin of the dwarf symptoms as well as of the mechanical malformations the beginning of the third week of embryonic life.

ACHONDROPLASIA [2]

In the monograph quoted in the above, we have represented Achondroplasic cases showing that besides the dwarf-phenomena in Achondroplasia a series of mechanical deformities are regularly present, viz. a dorso-lumbar arcuate kyphosis of the spine, kyphosis (and shortening) of the base of the skull, backward displacement of the hard palate and

[1] Cf. *Achondroplasia: its Nature and its Cause.* London: Ballière, Tindall & Cox.

[2] Cf. *Achondroplasia*, l.c.

tilting of its posterior end—in short that the physiological infolding which occurs in the third week of embryonic life, has been enhanced in the achondroplasic by external mechanical forces. This increased infolding must needs have taken place after the physiological infolding of the third week and before the physiological stretching of the sixth.

Now in the fifth week the flexible, scleroblastematous skeleton starts its change into cartilage. As is well known, this change is effected by rapid increase of the volume of the skeleton.

The skeleton in changing into cartilage, outgrows previous proportions; developing cartilage is a glutton among the tissues. Hence as the increased infolding in the Achondroplasic designates the period from the third to the sixth week as the time of its origin, the rapidity of growth of the skeleton during the formation of cartilage points out the fifth or sixth week as the time of great vulnerability of the skeleton. Hence both the mechanical malformations and the dwarf-phenomena indicate the fifth or sixth week as the time of origin of Achondroplasia.

Here again both groups of phenomena are explained by the assumption that the amnion lags behind in growth. The direct amniotic pressure infolding the embryo, the indirect or hydrostatic pressure, *i. e.* the pressure in the amniotic liquid, is enhanced. The blood is squeezed out of the fœtus and through the umbilical vessels to the placenta, whence it can enter into the province of enhanced pressure in the amniotic sac only with difficulty. The whole embryo suffers from hunger and the glutton among the tissues is first and most doomed to dwarfism.

Note that this difficulty for the blood to pass from the placenta to the amniotic cavity would not exist—or in a far less degree—in case the pressure in the *peri*amniotic space should be enhanced, *i. e.* by hydrochorion, because in that case the placenta would also be submitted to enhanced pressure. Hydrochorion, therefore, could not be taken as the cause of the dwarf-symptoms any more than it can be of the mechanical malformations in Achondroplasia. The pressure of hydrochorion would indeed act equally on all parts of the embryo and could never cause its infolding. (Cf. Postcript, p. 82, last paragraph.)

We are thus forced to exclude the chorion as the cause of Achondroplasia. On the other hand, we know no phenomena in this condition that are in contradiction with the assumption of its being produced by smallness of the amnion or by hydramnion. All the symptoms of Achondroplasia we have been able to study find a ready explanation by this assumption. The symmetry of the dwarf-phenomena, their gradation after the time of development of the parts (*i. e.* the fixation of fœtal proportions in the Achondroplasic), the frequent presence of other non-characteristic mechanical malformations as well as phenomena of growth-

stunting. For them, however, the interested reader may be referred to the monograph quoted above.

If we are right in assuming that amniotic pressure is the cause of Achondroplasia, the resemblance between Achondroplasia and "Rachitis" —great enough sometimes to lead to diagnostic errors—is accounted for by the fact that both owe their characteristic features to the operation of the same two principles. The enhanced hydrostatic pressure, compressing the whole of the—still flexible—fœtus and causing Ischæmia, is comparable to the injurious agents evoking the retardation of growth dealt with in the first part of this book. In both conditions the growth-stunting is proportional to the rapidity of growth of the parts. In both conditions, moreover, the differentiation shows extra-retardation, as is patent from the smallness of the bone-centres in the epiphyses and the short bones, *i. e.* the relatively considerable amount of unossified cartilage around these centres, as well as from the thickening of the growth-cartilages characteristic of Achondroplasia as well as of "Rachitis."

It might be objected that there is also a great *difference* between Achondroplasia and "Rachitis": Achondroplasia is present at birth, lasts throughout life undiminished and unaffected by medicaments, whereas "Rachitis" develops after birth, seems open to improvement by adequate treatment, and leaves its characteristic stamp in the adult only in the serious cases.

To this it should be observed that the process of normal growth which is stunted in both conditions, is determined by a series of factors, among others the condition of the digestive organs, the blood-glands, the bone-forming cells. In Achondroplasia the nocivity is acute and extremely serious, threatening immediate death; and affects chiefly—if not only—the last link of the chain of factors determining normal growth, viz. the growing cartilage-cells. In "Rachitis," on the contrary, the nocivity is more chronic, though far less serious, and certainly affects other growing tissues—for example the digestive tract and the blood-glands—as well as the growing bone. And the fact that "Rachitis" develops only after birth, may be due to maternal digestive organs and blood-glands acting as substitutes to those of the embryo or fœtus. But even if these points of difference in the causation of the two conditions could not be made responsible for the points of difference in their clinical picture, this would not interfere with their points of resemblance being brought about by the operation of the same biological principles laid down in this treatise.

MONGOLOID IDIOCY (MONGOLISM)

One hundred and twenty cases of Mongoloid Idiocy were examined by Dr. W. M. Van der Scheer, when Inspector of the Lunatic Asylums in Holland. He came to the conclusion that the pathogenesis of the condition had to be considered the same we had given for Achondroplasia, with the only difference that the amniotic pressure acts a little later, viz. in the sixth or seventh week of fœtal life. He says: "The assumption of smallness of the amniotic sac by which the physiological stretching

is arrested in the sixth or seventh week, may give an explanation of all symptoms of Mongoloid Idiocy.[1] This view is illustrated with Figs. 1 and 2, which by his kind permission have been put at our disposal.

Van der Scheer found the following mechanical malformations to be characteristic of Mongoloid Idiocy: a dorso-lumbar kyphosis of the spine, a flattening of the forehead and the upper part of the nose, smallness of the maxillary sinus, shortness and backward displacement of the hard palate, narrowness of the naso-pharyngeal cavity, shallowness of the eye-sockets, shortening of the base of the skull, flattening of the occiput.

" How can the development of the dorso-lumbar kyphosis be thought otherwise than by excessive infolding of the fœtus? " Van der Scheer asks. And it cannot raise wonder that the same pressure should also

FIG. 1.

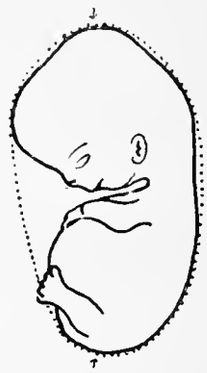


FIG. 2.

compress and shorten the head, thus causing *hyperbrachycephaly*, which is almost pathognomonic of Mongoloid Idiocy (Van der Scheer).

The seventh week is a period of rapid growth to the brain. It then outgrows previous proportions, which determines its vulnerability at this time, and thus the dwarfing of the brain, the Idiocy, by the direct pressure acting on it.

Besides these results of direct pressure, Mongoloid Idiocy regularly shows dwarfism of other parts. The Mongoloid Idiot is under-sized. There is Micromelia with shortness of hands and feet. The fingers and toes are too short. The line connecting the tip of the toes is almost at right angles to the axis of the foot. In short the extremities of the Mongoloid Idiot show some or all of the characteristics of the Achondroplast. Thus an intimate relation appears to exist between Mongoloid Idiocy and Achondroplasia. And this also is patent from the fact that Mongoloid Idiocy and Achondroplasia show an affinity for the

[1] Dr. W. M. Van der Scheer, *Over Mongolismus. Ned. Maandschrift voor Verloskunde*, 1918.

same congenital malformations, as Harelip, Micrognathy, Clubfoot, and others.

The "Mongoloid" position of the eyelids is caused by dwarfism or absence of the nasal bones, the frontal bones substituting the defect by sending out processes from lateral and above in a medial and downward direction (Dr. Nieuwenhuysen), and the covering tissues following the direction of the underlying bony parts.[1] The line connecting the highest part of the border of the upper eyelid with the lowest point of the lower lid normally crosses the binocular axis at right angles. In Mongoloid Idiocy it is directed laterally and downward (Van der Scheer). Thus the "Mongoloid" symptom finds a simple explanation from the dwarfism or absence of the nasal bones.

A number of secondary symptoms, not present at birth, but developing in after life, are attributed by Van der Scheer to dwarfism of the mid-brain (especially the interpeduncular region) and pituitary body. The smallness of these parts has been ascertained in six cases that have come to autopsy. For these secondary symptoms we must refer the reader to the original article. For the present it may suffice that all symptoms of Mongoloid Idiocy find explanation by the application of the principles laid down in the Introduction of this treatise.

DYSOSTOSIS CLEIDO-CRANIALIS

Since 1897, when Marie and Sainton recognized Cleido-cranial Dysostosis as a characteristic hereditary congenital malformation, and gave it its name, about a hundred cases have been observed by Carpenter, Schleuthauer, Hultkranz, Pinard and Varnier, Fitz-Williams, Gianettaso, Raubischek, Maldaresco and Parhon, Paltauf, La Chapelle[2] and many others, confirming their observations. Besides La Chapelle's five cases in one family, we have ourselves observed three, *i. e.* in all eight, cases in three families which are not mutually related.

As is expressed by the name, two symptoms characterize Dysostosis Cleido-cranialis (see Figs. 3–10):

(1) The retardation of development of the frontal bones, *i. e.* of the closure of the large fontanel, which is enlarged and may remain open for life;

(2) The fact that one or both clavicles are defective. They often present the characteristics of a pseudarthrosis. But all transitions have been observed, from a pseudarthrosis of one of the collar-bones

[1] *Psychiatrische en neurologische bladen*, 1918. Feestbundel Winkler.

[2] To La Chapelle's thesis (Leiden, 1918) we are largely indebted for our knowledge of the literature of Dysostosis.

FIG. 3.—(Son Mev.) Dysostotic.

FIG. 4.—(Mother Gro.) Dysostotic.

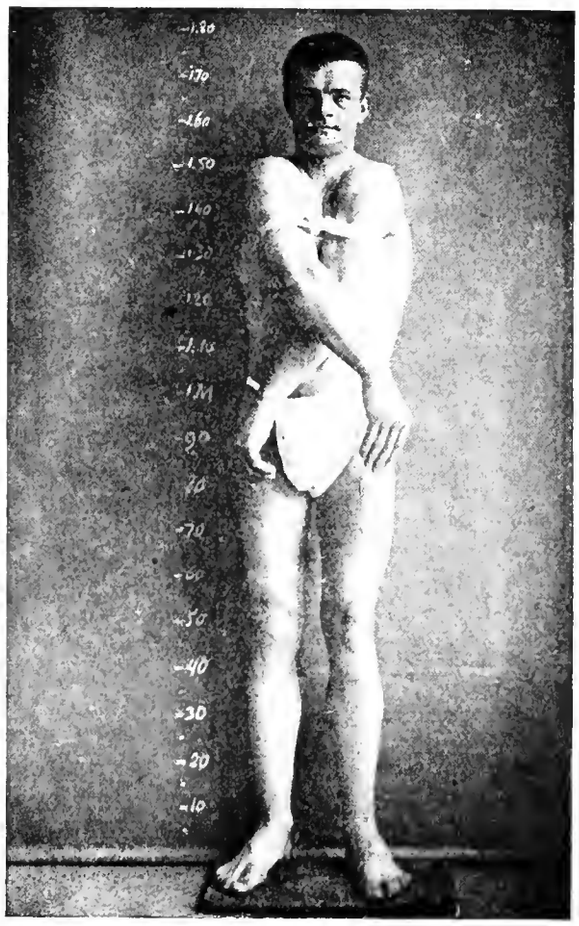


FIG. 5.—(P. Gro.) Dysostotic.

FIG. 6.—(A. Gro.) Dysostotic.

FIG. 7.—(Ja. Gro.) Dysostotic.

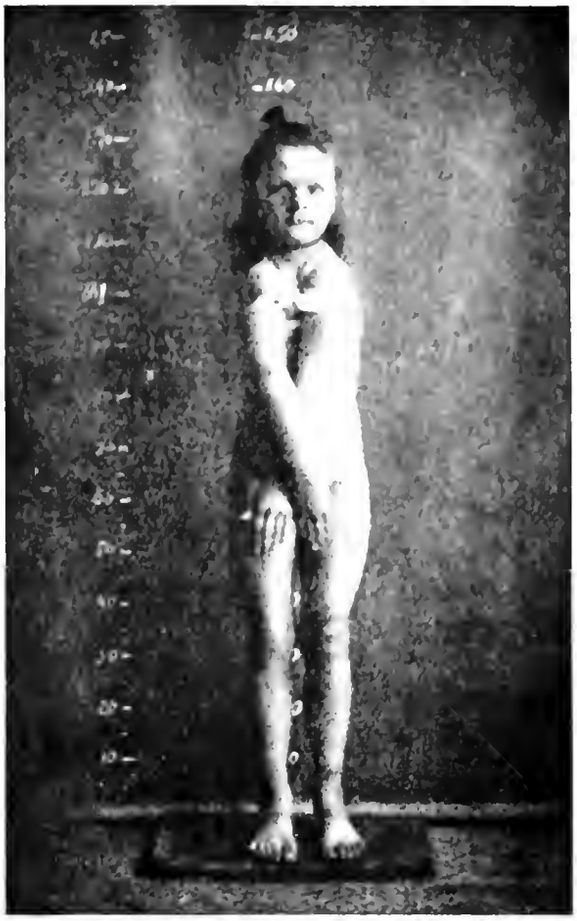


FIG. 8.—(G. Gro.) Dysostotic.

FIG. 9.—(Mo. Denh.) Dysostotic.
(Left clavicle unaffected).

FIG. 10.—(Daughter Denh.) Dysostotic.
(Left clavicle unaffected).

to the absence of the acromial or sternal end or even the total absence of both clavicles.

Around these two symptoms are grouped a number of others, constant as well as inconstant, with which we will deal by-and-by. We will first direct attention to two symptoms which we have found without an exception in seven cases we have been able to examine. These cases belong to three families not mutually related.

The two symptoms are :

(*a*) *A shortening of the intermediate and terminal phalanges of the toes. The widened ends of the latter are missing as though they had been*

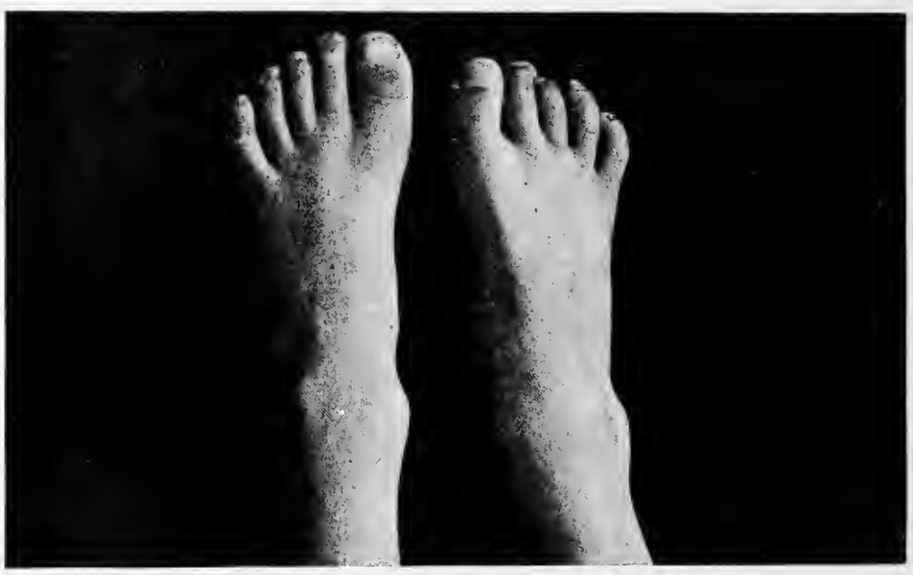


FIG. 11.—(Son Mev.) Dysostotic.

nibbled off. This has hitherto escaped attention and betrays itself clinically by shortness of the toes and of the nails [1] (cf. Figs. 11 and 12 with Fig. 13; and Figs. 14 and 15 with Fig. 16). The terminal phalanges of the fingers also show a "nibbling" (Fig. 17) or a thinness and abnormal translucency to X-rays (cf. Fig. 18), with the normal condition of Fig. 19. But this latter symptom is not always obvious, and in all cases the terminal phalanges of the fingers are better developed than those of the toes.

It is probable that the intermediate and terminal phalanges of the toes may have exhibited this shortening not only in our own cases but in others, and that this is really a constant symptom which has hitherto escaped attention. In that case the condition might be properly termed Dysostosis Cleido-cranio-(digitalis). At all events in dealing with the

[1] Our eighth case (Fig. 10) suffering from epilepsy, was not in a state to bear an X-ray examination, and so the shortness of her phalanges has not been demonstrated skiascopically.

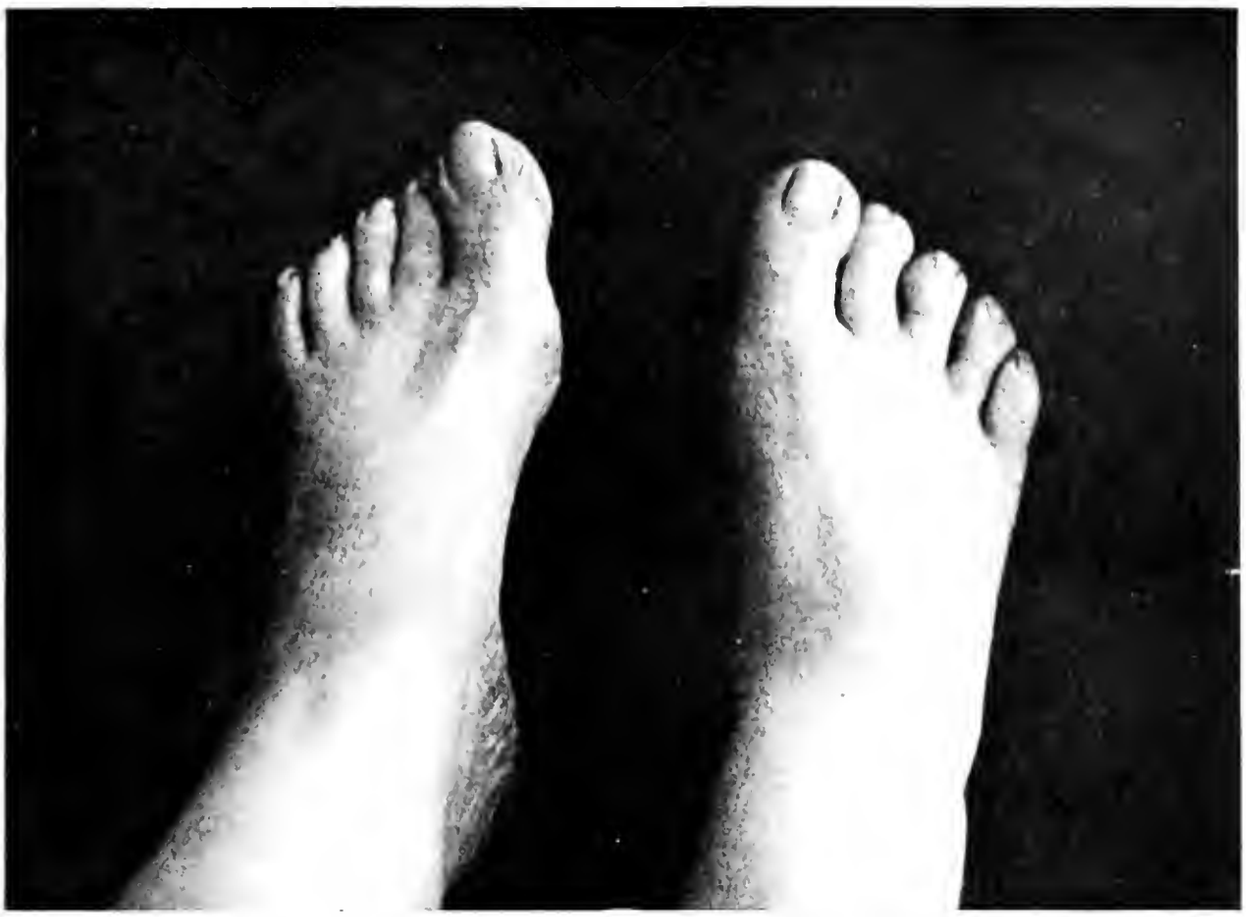


FIG. 12.—(Mother Gro.) Dysostotic.

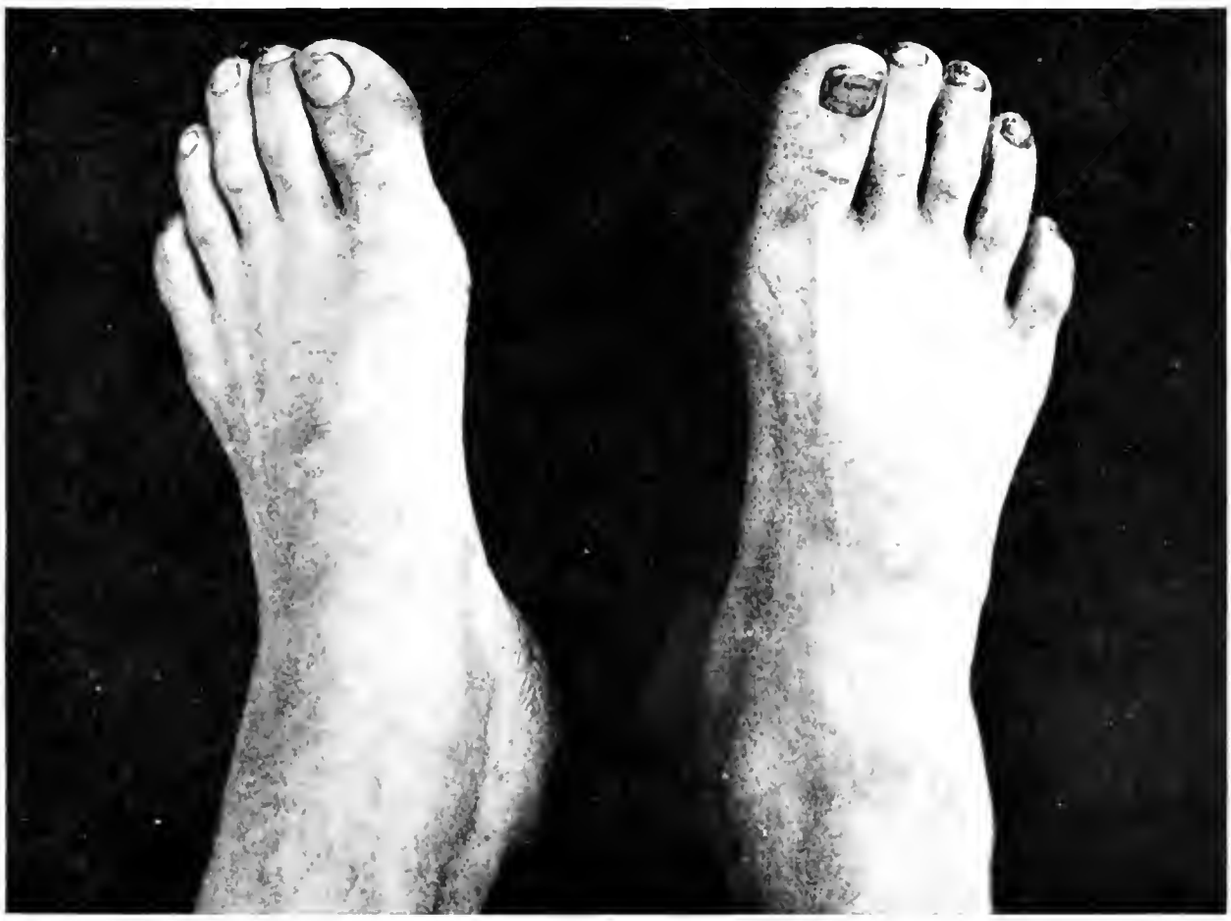


FIG. 13.—(Jo. Gro.) Normal.

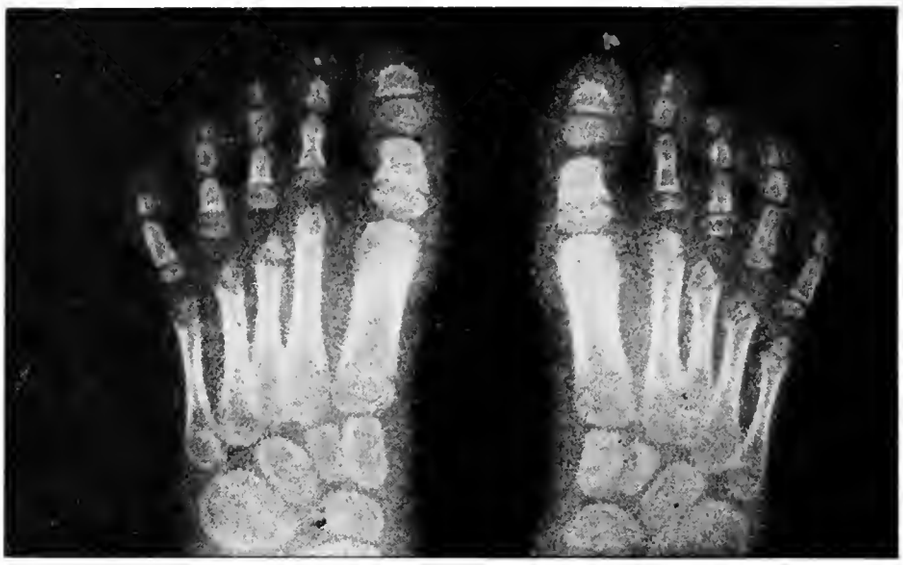


FIG. 14.—(Son Mev.) Dysostotic.

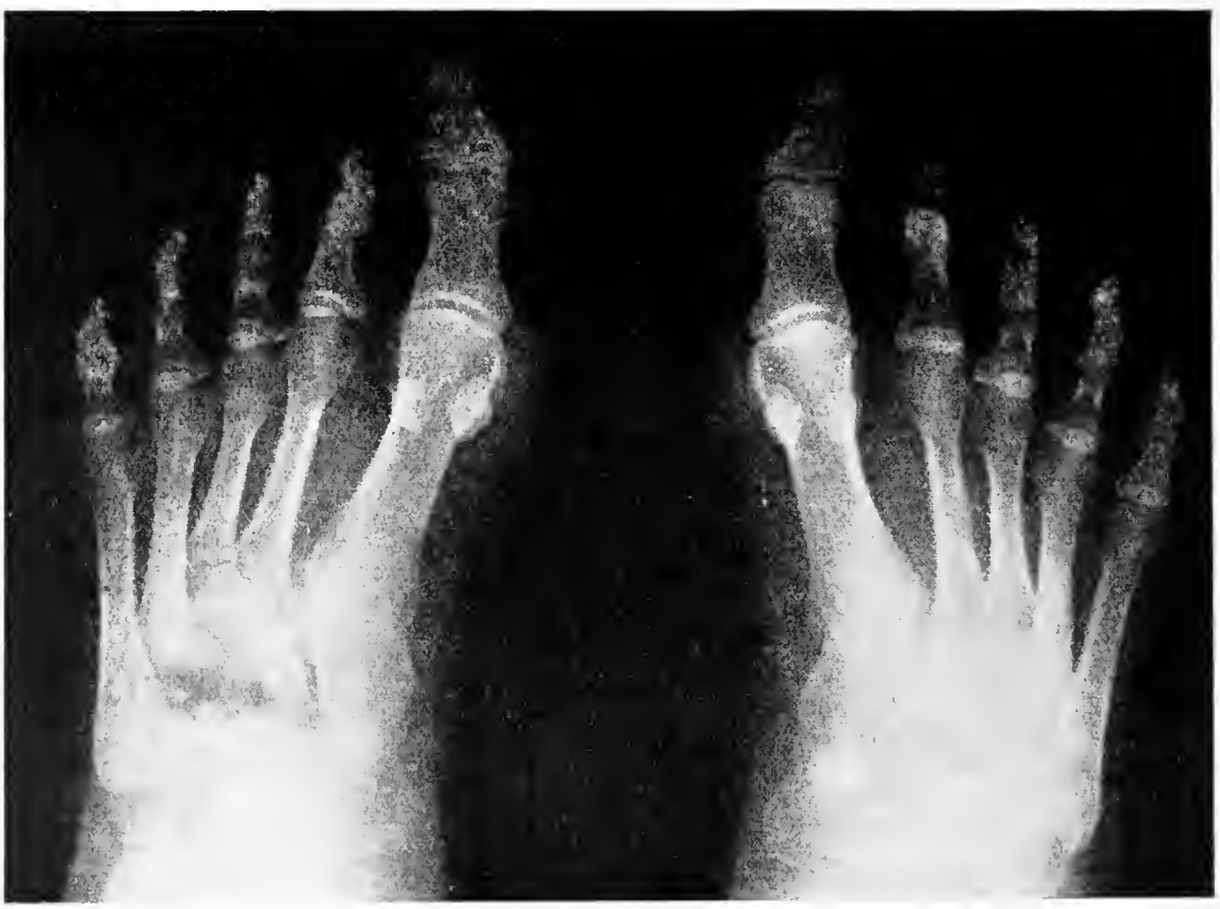


FIG. 15.—(Mother Gro.) Dysostotic.

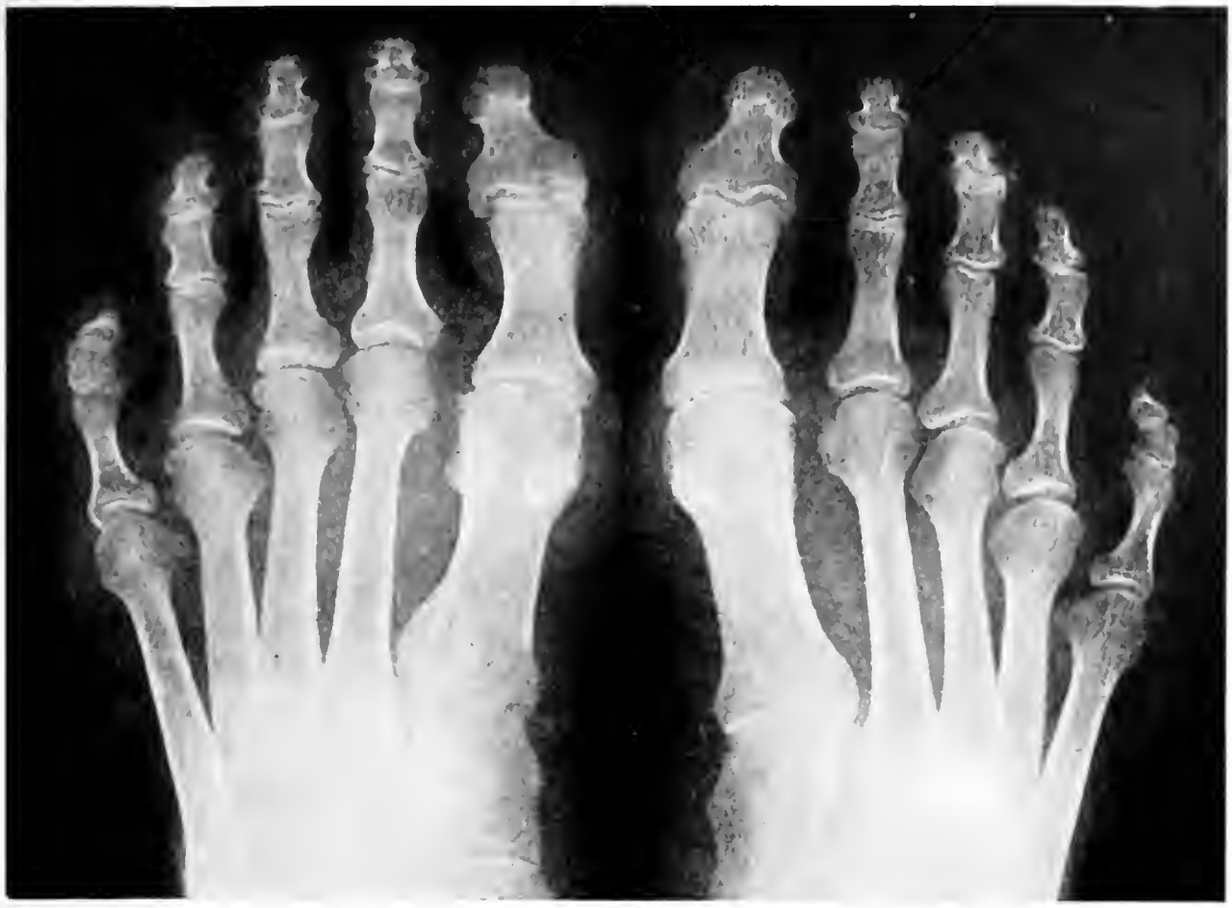


FIG. 16.—(Jo. Gro.) Normal.

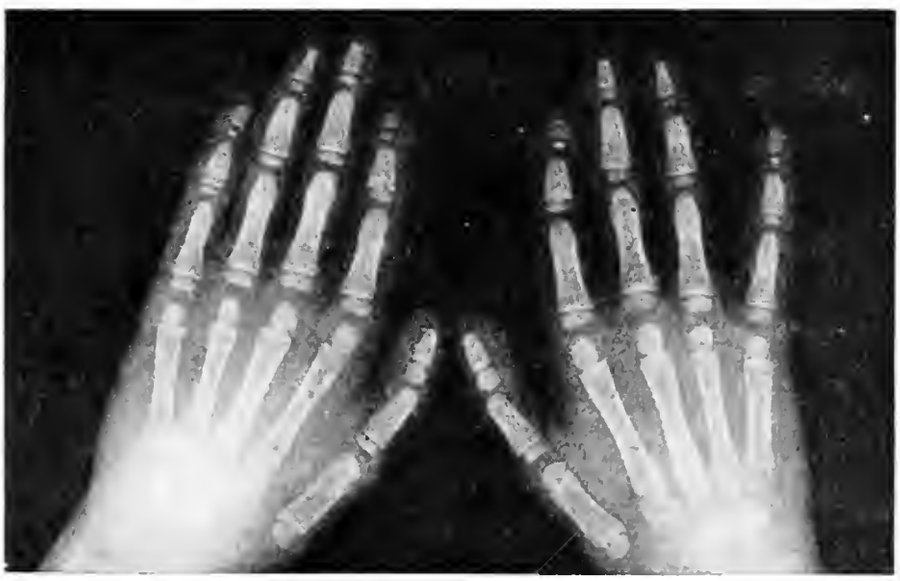


FIG. 17.—(Son Mev.) Dysostotic.

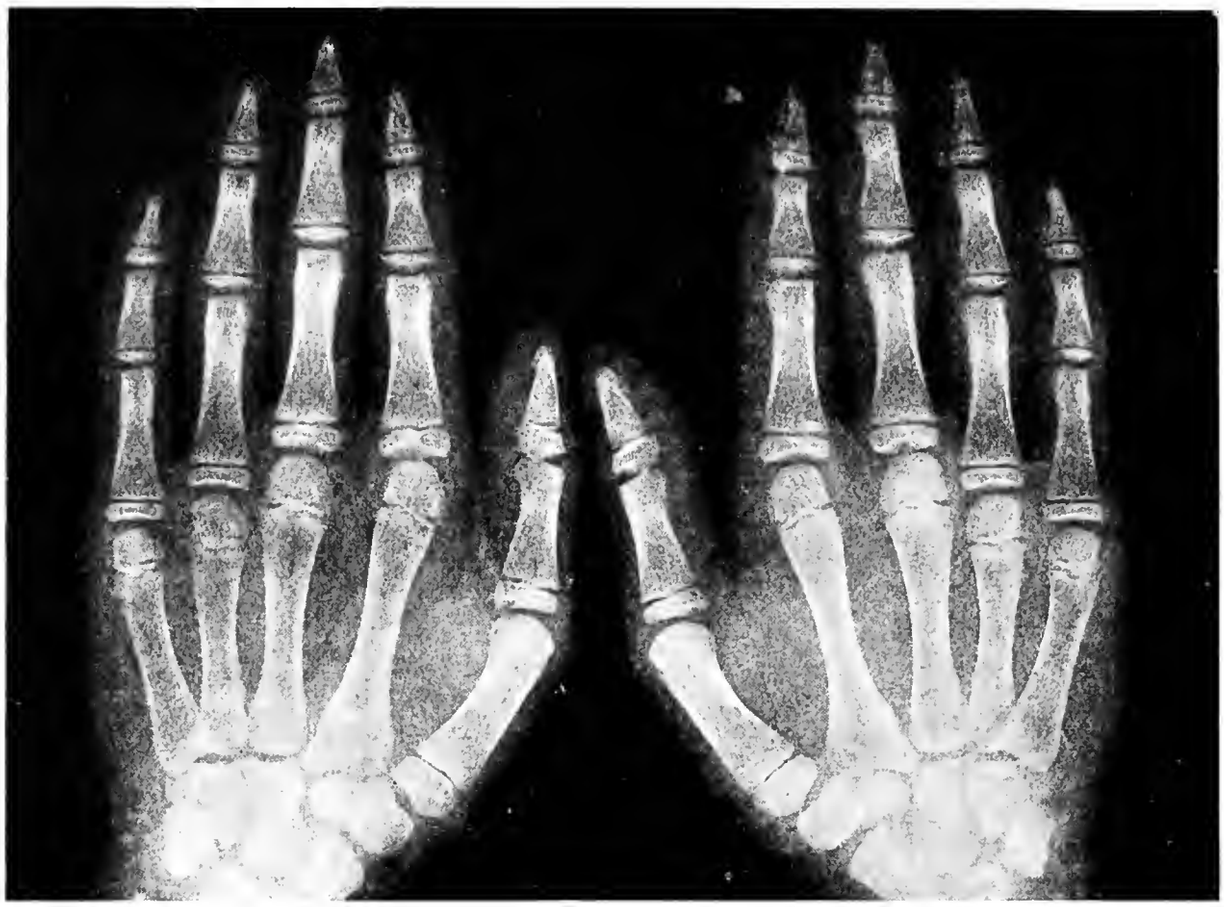


FIG. 18.—(Ja. Gro.) Dysostotic.

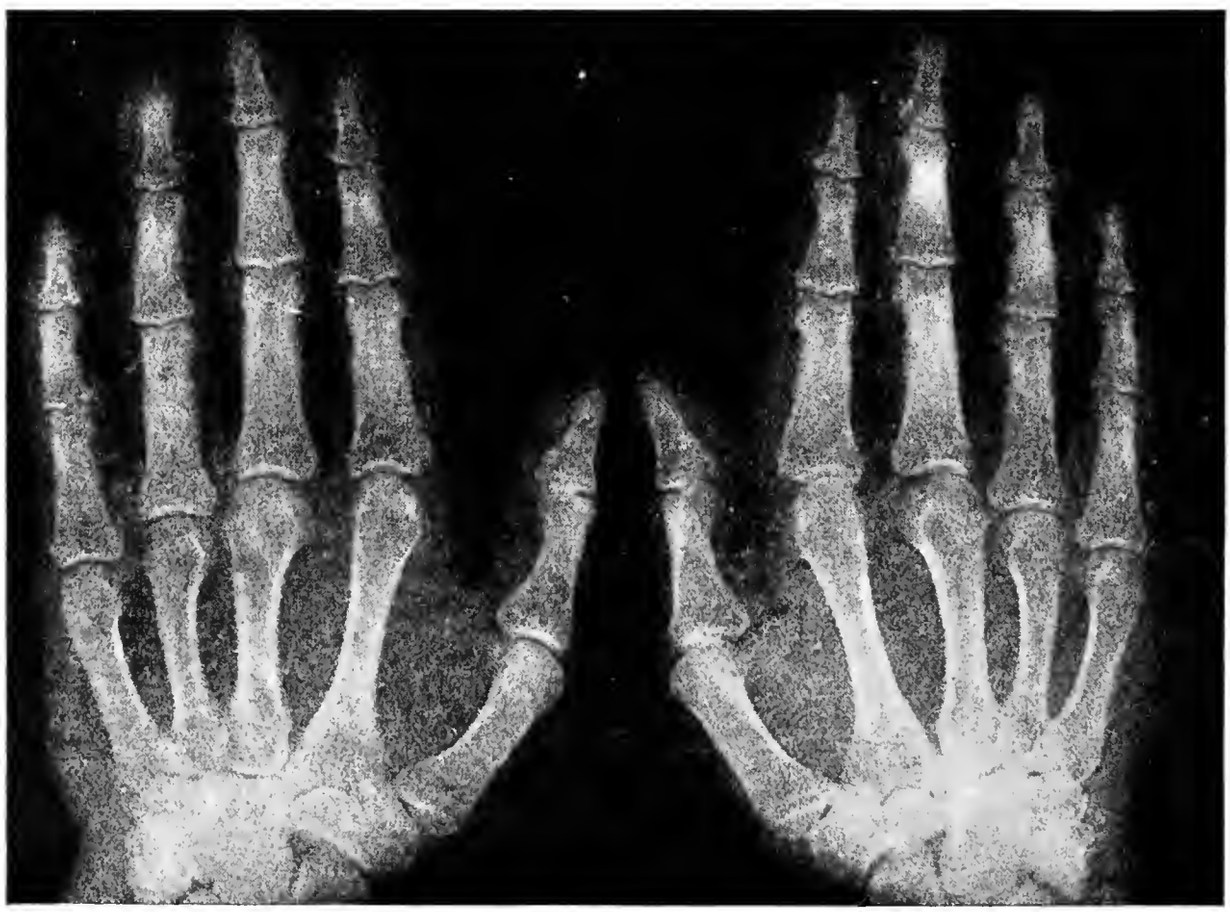


FIG. 19.—(Jo. Gro.) Normal.

pathogenesis of the condition, this symptom will demand an explanation as well as the rest.

(*b*) *A bilateral narrowing of the chest.* (See Fig. 20.)

The ribs of all our cases[1] of Dysostosis Cleido-cranio-(digitalis) are less curved and more drooping than normally (cf. Figs. 21 and 22 with Figs. 23 and 24). The symptom of bilateral narrowing of the chest has been mentioned in literature ere now, only its constancy, which it seems justified to assume, from our experience, has not been recognized.

FIG. 20.—(Son Mev.) Dysostotic.

The bilateral narrowing of the chest can be considered only as a mechanical malformation, *i. e.* as a malformation produced by mechanical forces, whilst the shortening of the terminal phalanges of the toes is to be considered as a retardation or arrest of growth. We shall see later on that all symptoms of Dysostosis Cleido-cranio-(digitalis) bear the characteristics of either of these groups, *i. e.* of mechanical malformations or phenomena of stunting of growth. These two groups will prove to be intimately related, so that in the description of one group we shall meet with symptoms of the other.

[1] *I.e.* the seven X-rayed cases.

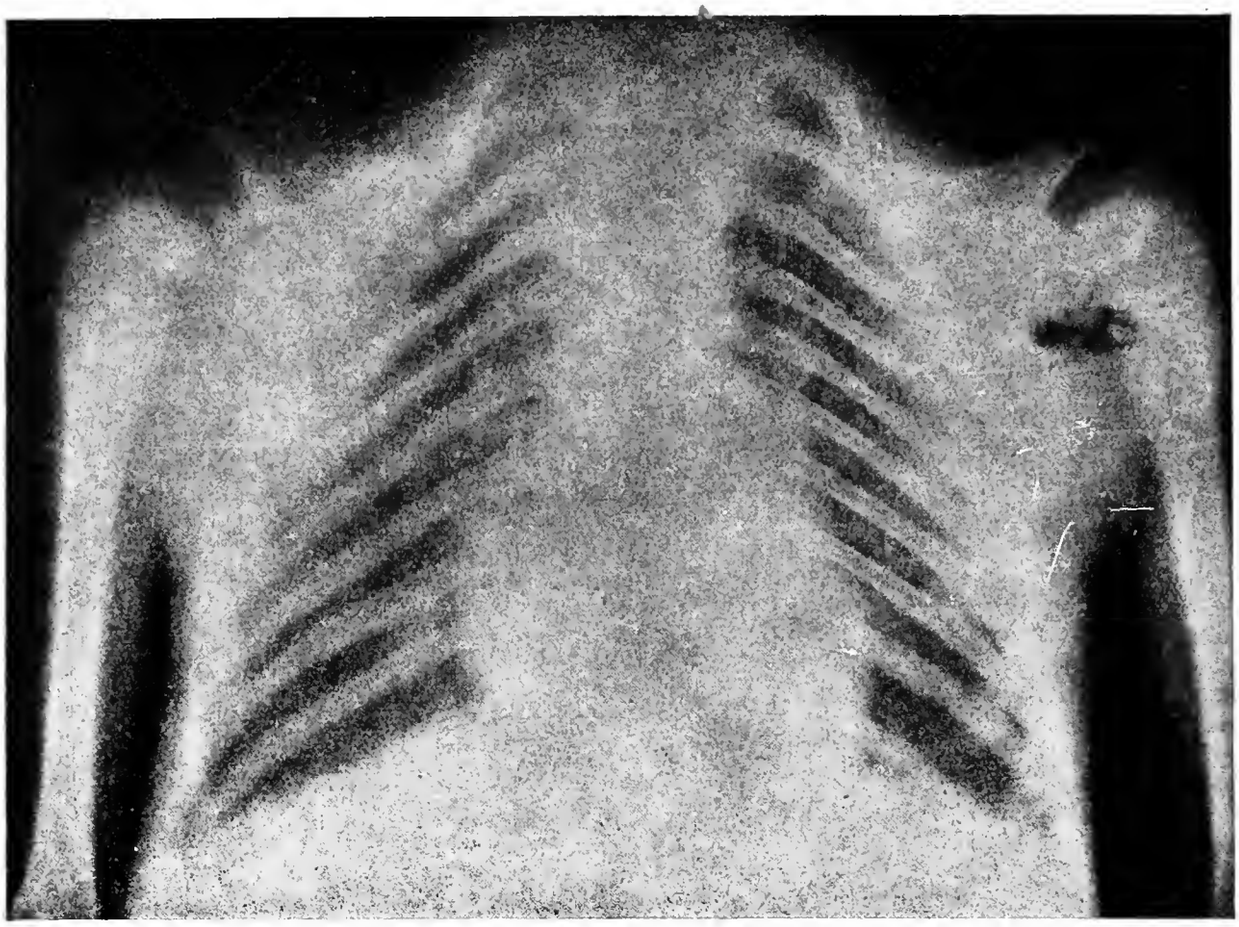


FIG. 21.—(Son Mev.) Dysostotic.

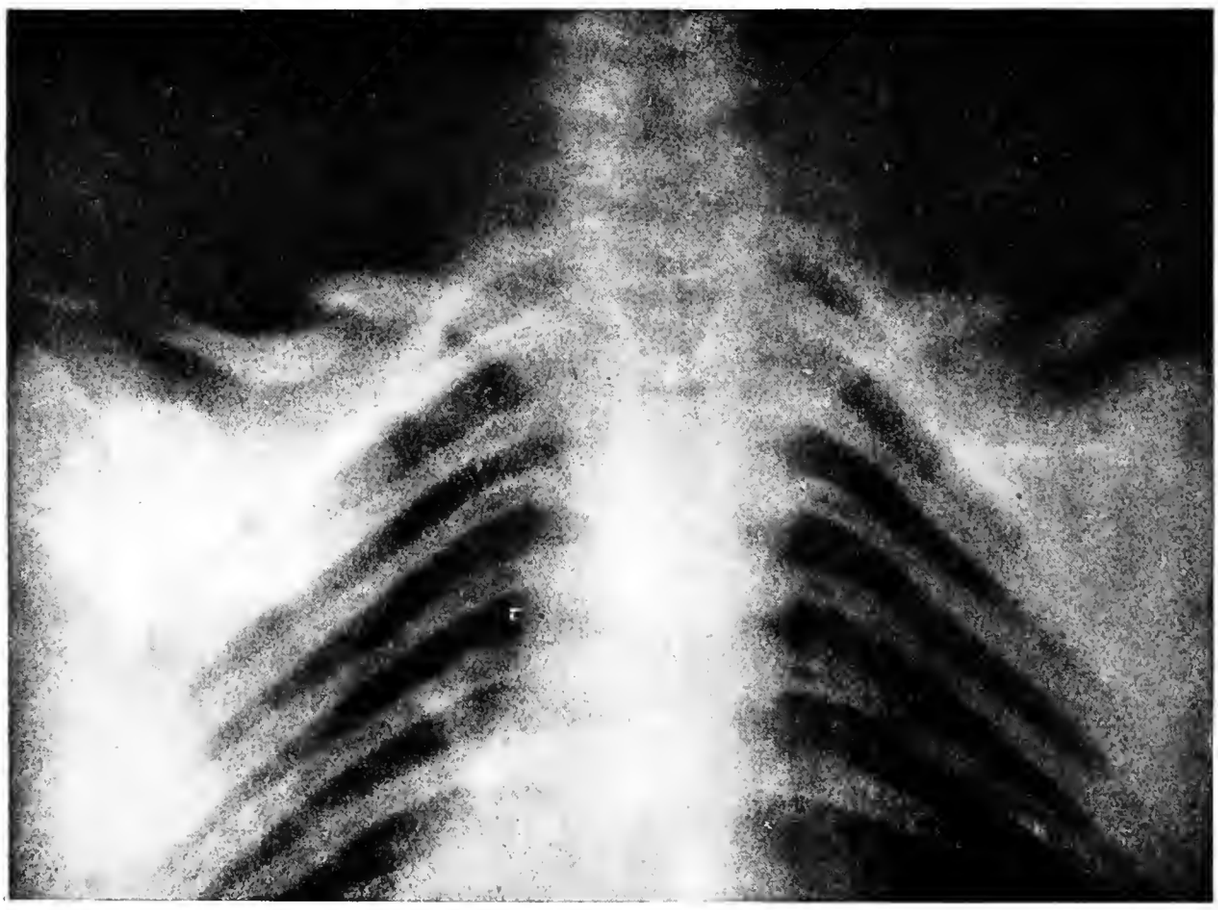


FIG. 22.—(A. Gro.) Dysostotic.

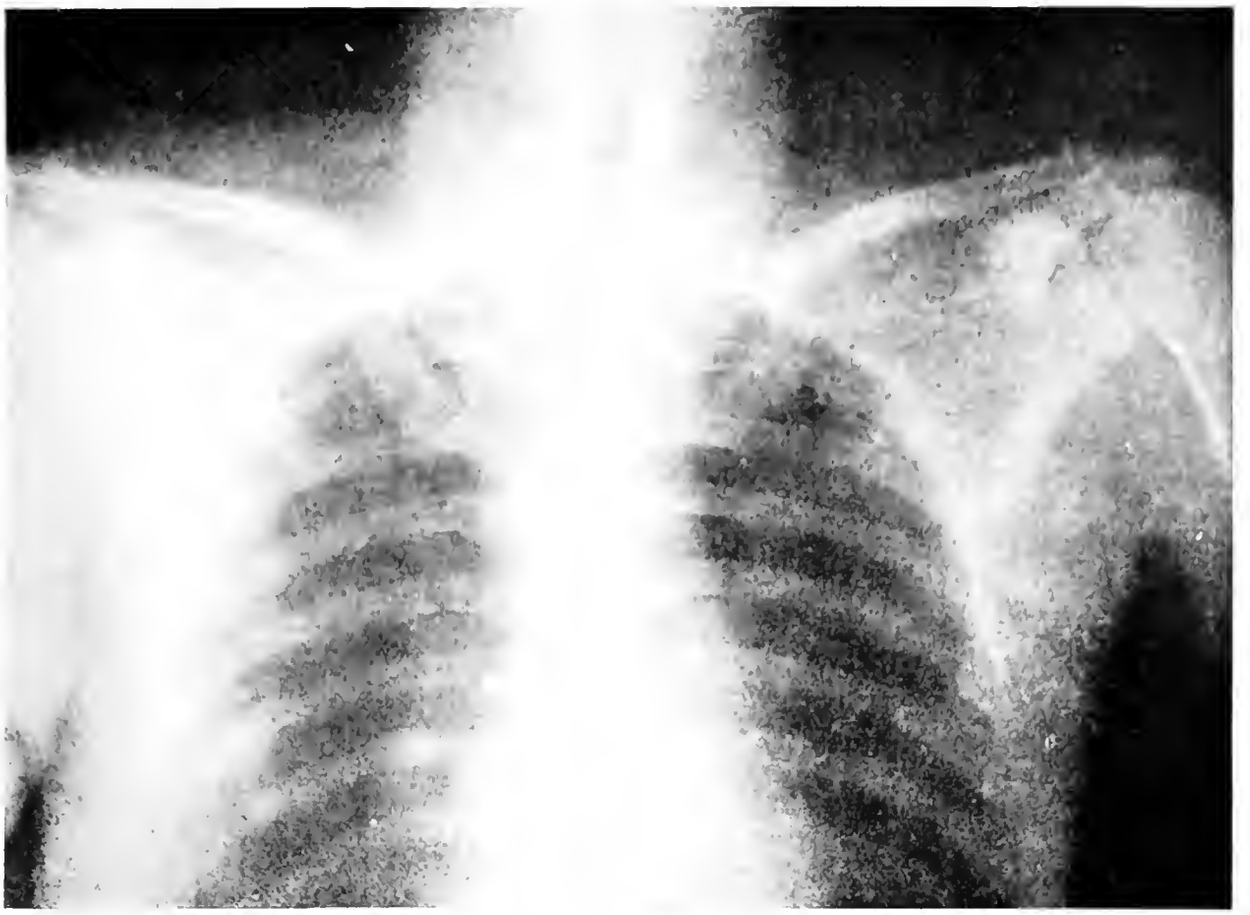


FIG. 23.—(Father Mev.) Non-dysostotic.

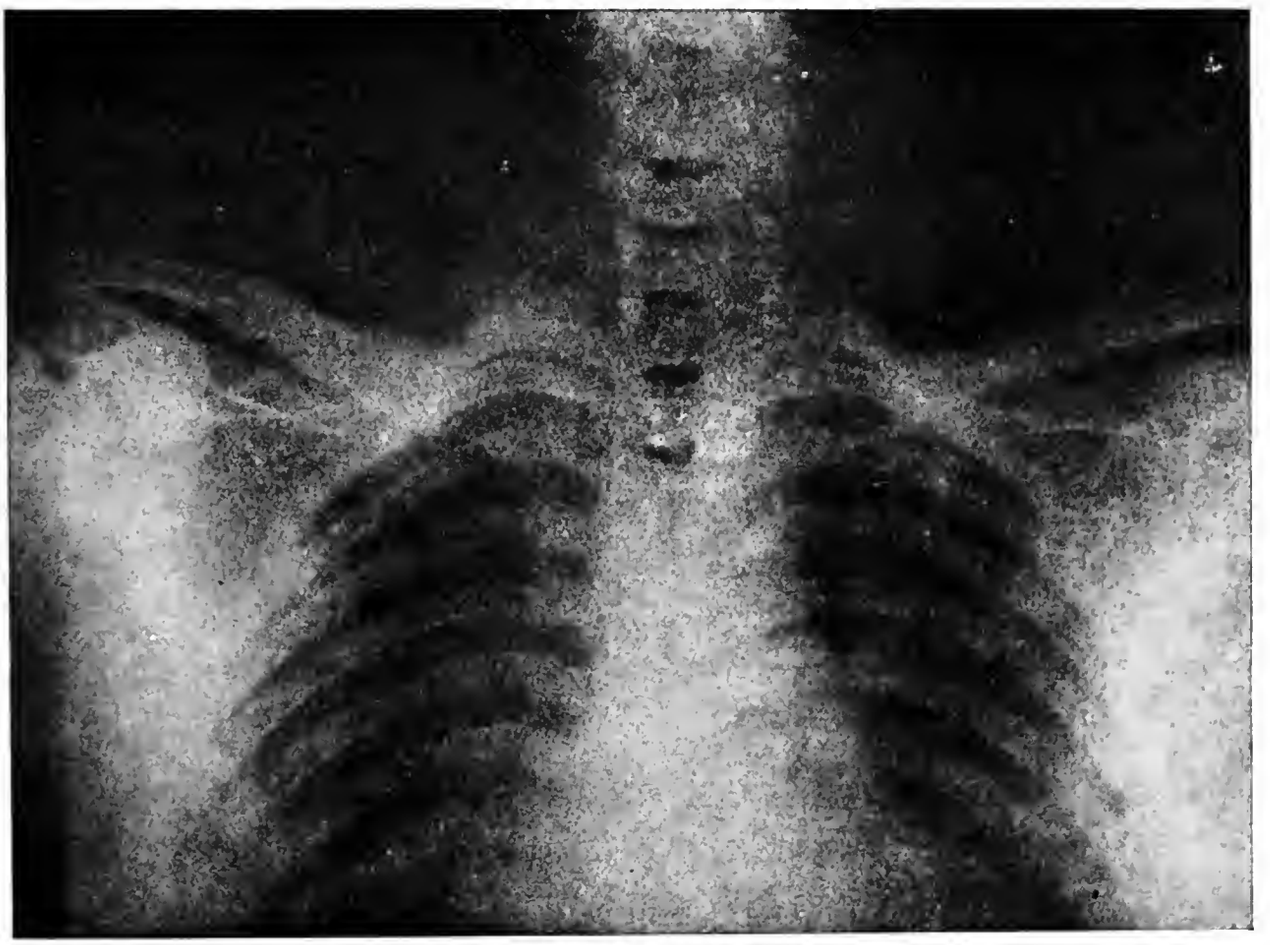


FIG. 24.—(Jo. Gro.) Normal.

Besides the bilateral narrowing of the chest the subject of Fig. 3 shows narrowness of the base of the skull. The squamæ of the temporal bones are directed obliquely from below upwards so that the ears, instead of running parallel, converge in a downward direction (see Fig. 20). The face even seems to participate in this bilateral narrowing. The arch of the hard palate is too narrow and too high, ogive-shaped. The antero-posterior skiagram of the skull (not represented) also shows this bilateral narrowing of the face. But be this as it may, the arch of

FIG. 25.—(Mo. Gro.) Dysostotic.

the palate is too narrow; and—what the figures fail to show—on palpation the jugal or malar bone appears to be defective. This symptom is not rare. By the side of the mechanical malformations it appears as a phenomenon of growth-stunting.

Seen from the side, the face of the subject of Fig. 3 shows a protrusion of the maxilla and the upper lip contrasting with the profile of the seven other cases of Dysostosis we have observed. In them the maxilla projects forward less than normally, so that in extreme cases the profile of these subjects is crescent-shaped (see Fig. 25). This deformity is more obvious still in the skiagram taken from the side of

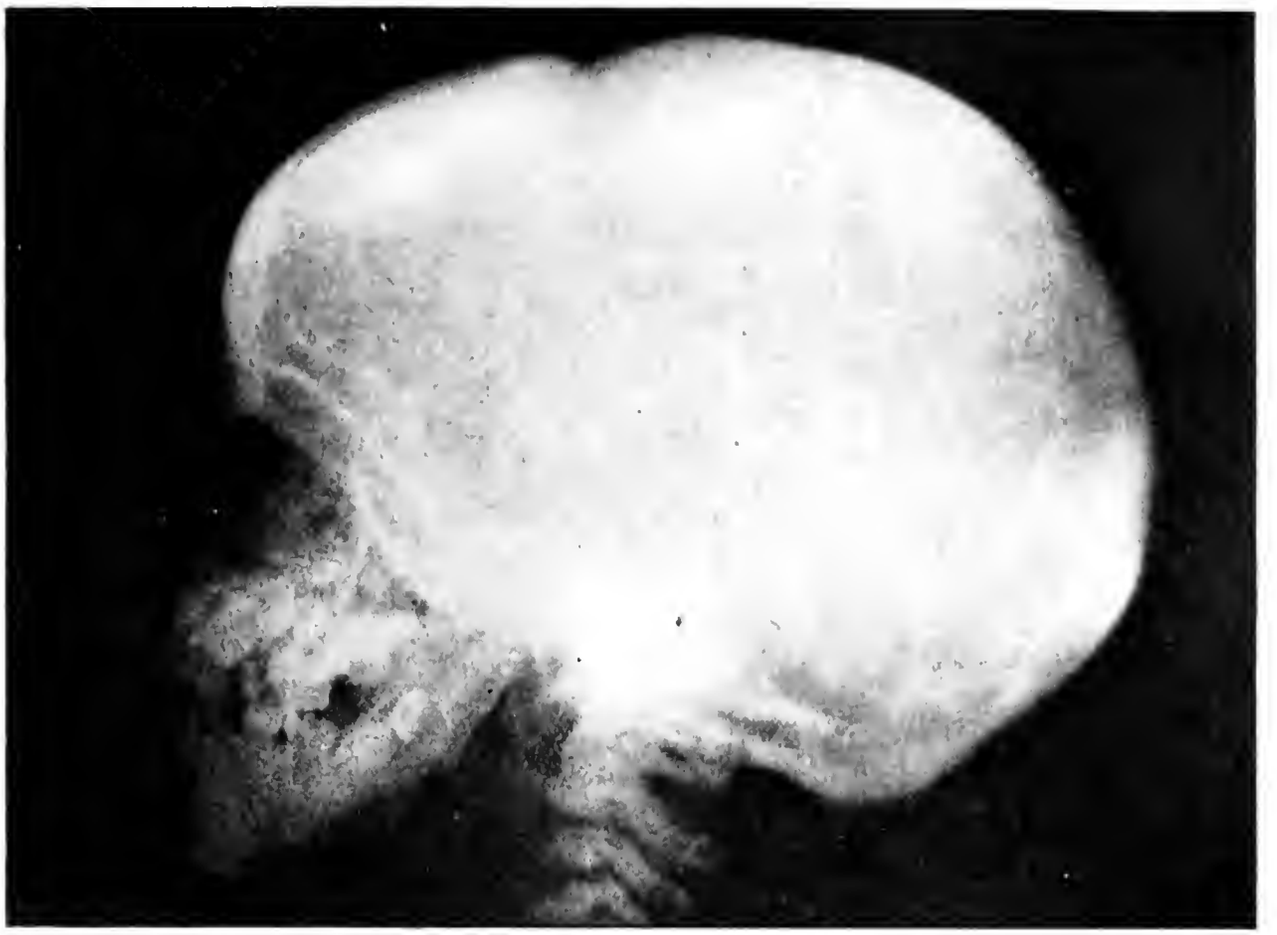


FIG. 26.—(Son Mev.) Dysostotic.

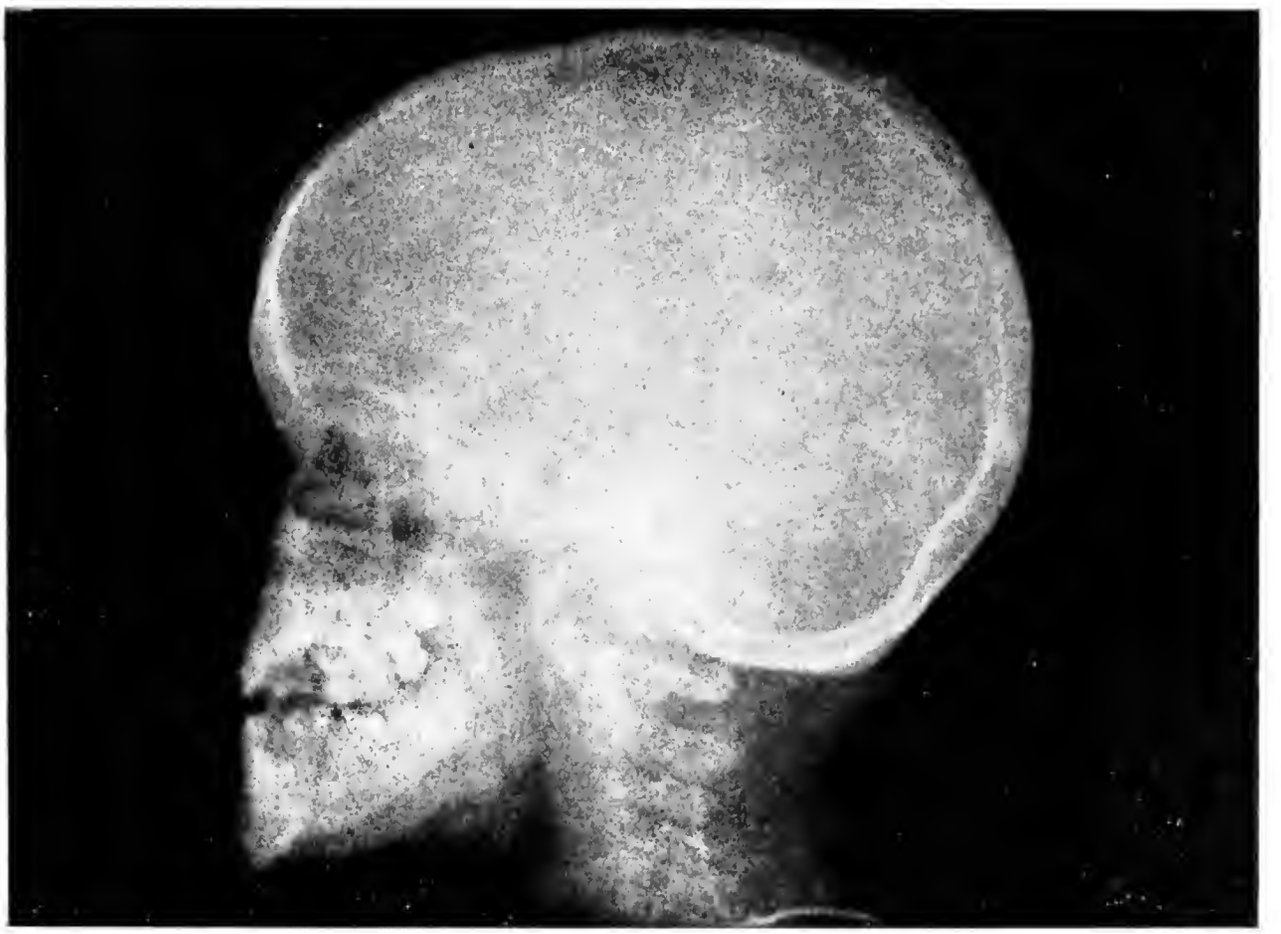


FIG. 27.—(Ja. Gro.) Dysostotic.

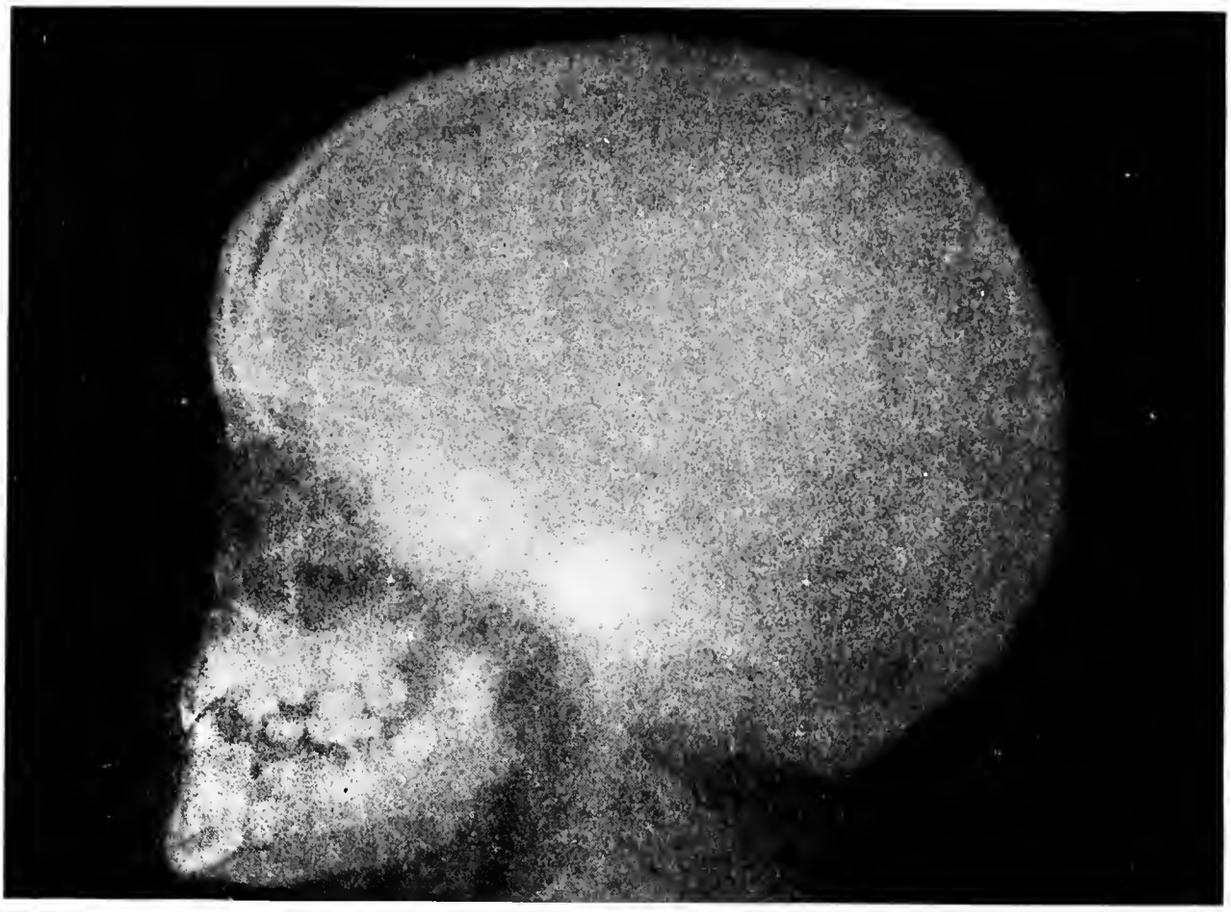


FIG. 28.—(G. Gro.) Dysostotic.

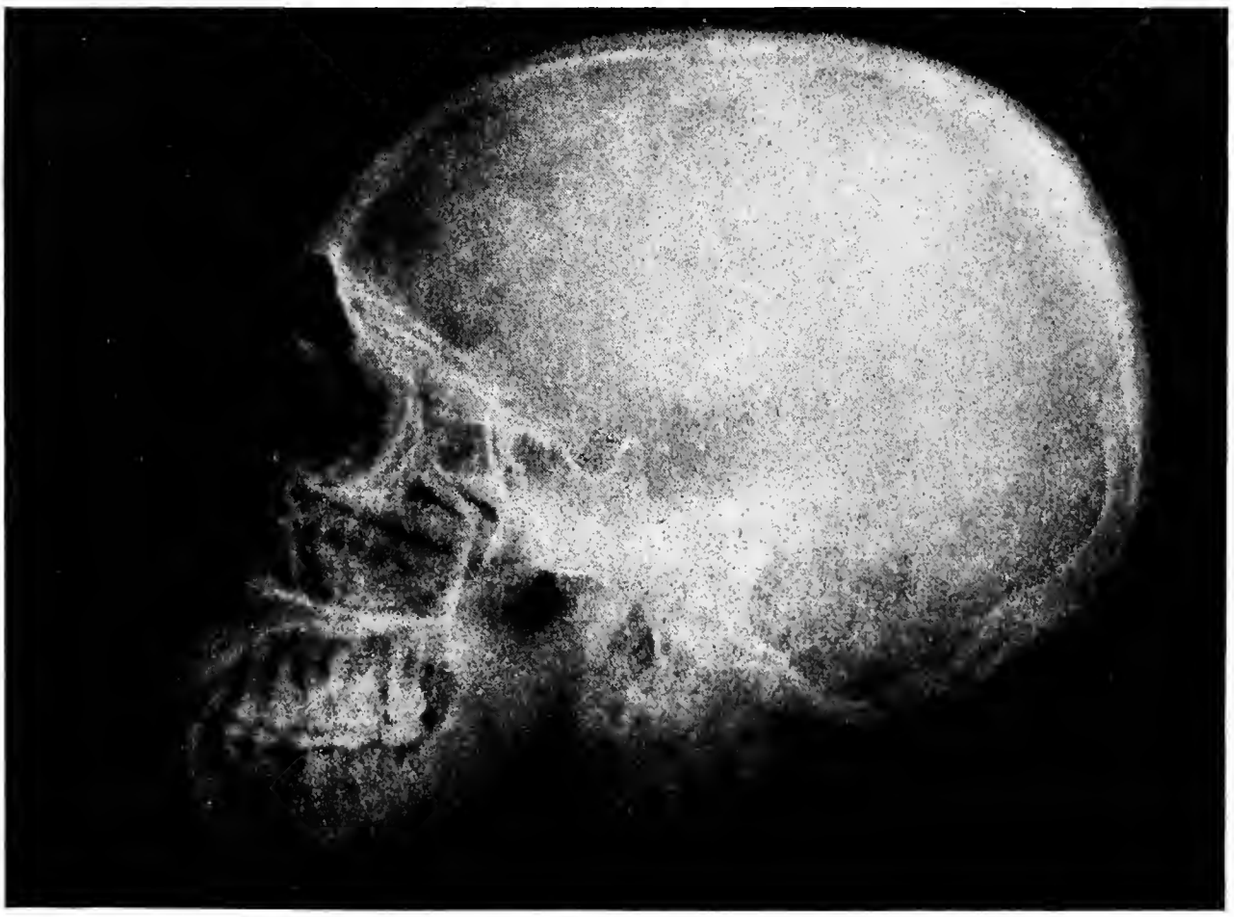


FIG. 29.—(Jo. Gro.) Normal.

the skull (cf. Figs. 26, 27 and 28 with the normal subject of Fig. 29).

The skeleton of the face appears moreover to be displaced backward and upward with regard to the brain-pan. The posterior part of the maxilla appears to be turned upward, the hard palate being tilted, so that the angle it forms with the base of the skull is enlarged, while at the same time the posterior nares are smaller than normal. The base of the skull appears to be pressed in or dented; it shows a kyphos or angular deformity. The other Dysostotic skulls show the same phenomenon in varying degrees. Moreover, the base of the skull seems shortened. The frontal bone (from about the metopic point downward to the nasion) is directed backward, the occipital squama (from about the lambda downward to the inion) shows a more forward direction than normally. All these symptoms have been described by other authors. It has also been pointed out that in connection with the Kyphos Baseos Cranii the posterior part of the Clivus Blumenbachii comes too near to the vertical line, and the posterior border of the occipital foramen appears to be lowered. This foramen, therefore, opens in Dysostotic skulls from behind forwards rather than from above downwards. Note also that the angle between the horizontal and the ascending ramus of the mandible is too obtuse. All these symptoms are characterized by displacements of parts; they are mechanical malformations. They are accompanied by smallness or absence of the frontal sinuses (cf. Figs. 26, 27 and 28 with Fig. 29) and smallness of the maxillary and sphenoid sinuses. In the subject of Fig. 3 the absence of the frontal sinuses reveals itself even in the absence of the supraciliary arches, which gives an "incredulous" expression to the face. It is open to discussion whether the absence (or smallness) of the sinuses is to be ranged among the mechanical symptoms or amongst those of growth-stunting. But the excessive dimensions of the large fontanel and its late closure, as well as the defective development of the jugal or malar bone, and the absence of the nasal bones, which is not at all rare, are indisputably characterized by retardation or arrest of growth.

All the mechanical malformations of the skull we have described, are met with in Achondroplasia. Those of the base of the skull are generally known in Achondroplasia.[1] Some of them may be seen or presumed in Fig. 30. Furthermore, the shortness of the extremities, which constitutes the most obvious symptom in Achondroplasia, is present—though in less degree—in some of the cases of Dysostosis (see Figs. 4, 5, 6, 9, 10). The father of the subject of Fig. 3 (see Fig. 31),

[1] Cf. *Achondroplasia, its Nature and its Cause.* Brill, Leiden; and Ballière, Tindall & Cox, London, 1912.

though not showing the characteristic complex of symptoms of Achondroplasia, has too short extremities. The body-height of Dysostotic subjects has often been described as being below the normal. Body-heights of 1·10 mm. (Raubischek), of 1·43 mm. (Couvelare), of 1·46 mm. (Hultkranz), of 1·48 mm. (Fuchs), of 1·51 mm. (Pinard and Varnier), of 1·52 mm. (Hamilton) have been observed, and as a rule Dysostotic subjects are

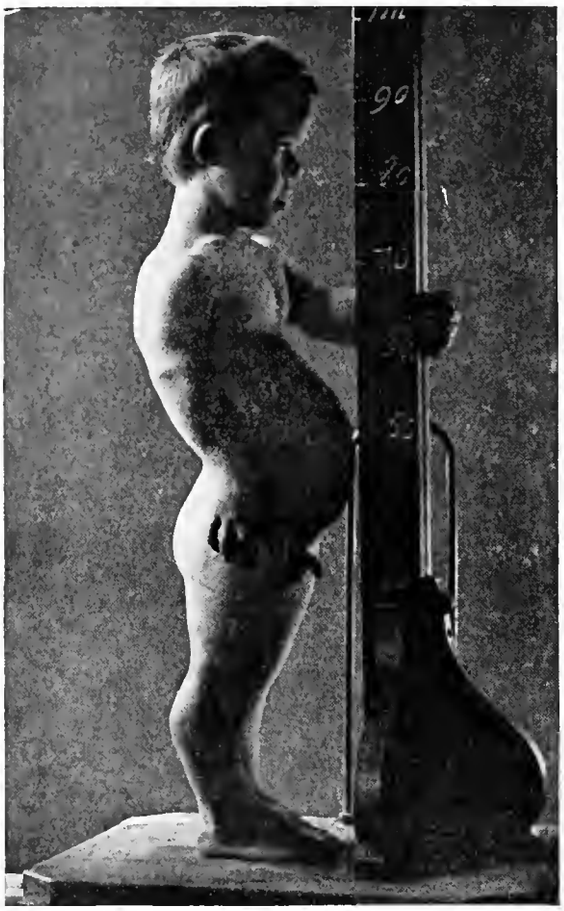


FIG. 30.—Achondroplast.

FIG. 31.—(Father Mev.) Father of the Dysostotic subject of Figs. 3 and 20. Non-dysostotic, yet showing the "*Syndrome of the short extremities.*"

smaller than their brothers and sisters. Finally, the dwarfing of the intermediate and terminal phalanges of the toes, the shortness of the toes, the narrowness and translucency of the terminal phalanges of the fingers, which we observed in Dysostosis, are present in the Achondroplasic as extra-dwarfism of these parts (see Figs. 32, 33 and 34, the feet and hands of Fig. 30). Hence Dysostosis cleido-cranio-(digitalis) shows indisputable relations to Achondroplasia.

In the above we have argued that all the symptoms of Achondroplasia may be explained by the assumption that the amnion, remaining too

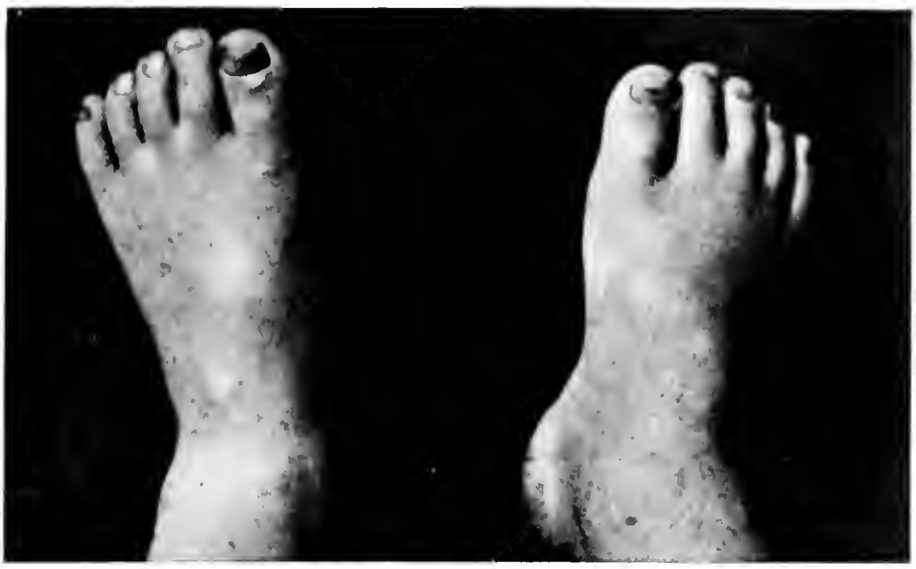


FIG. 32.—Achondroplasic feet (of FIG. 28).

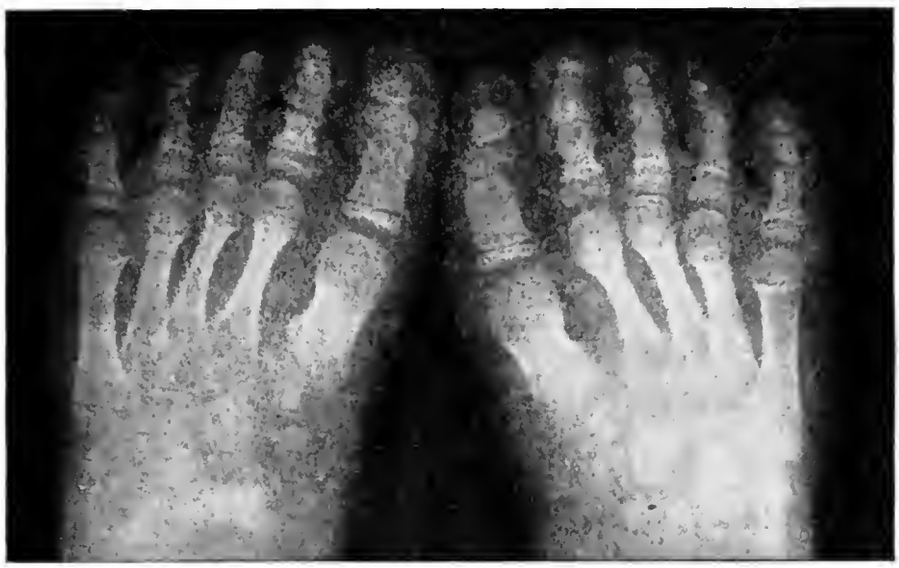


FIG. 33.—Achondroplasic feet (of FIG. 28).

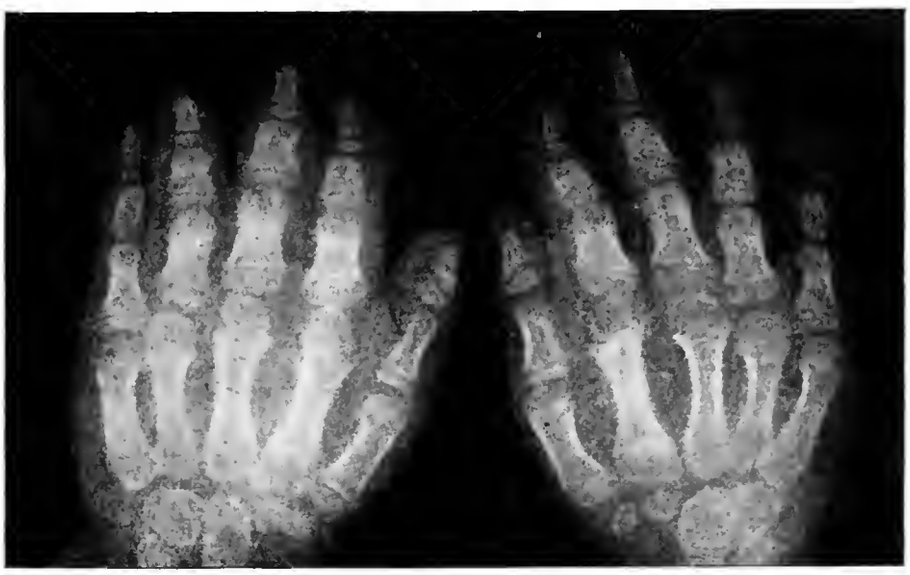


FIG. 34.—Achondroplasic hands (of FIG. 28).

small, enhances the normal infolding of the embryo in the fifth or sixth week of embryonic life; that it at the same time increases hydrostatic pressure inside the amniotic sac and squeezes the blood out of the fœtus during the formation of its cartilaginous skeleton. We will now try to prove that *all the symptoms of Dysostosis may be explained* in an equally simple way, *if we assume that smallness of the amnion infolds the fœtus during the eighth week of fœtal life.* Whilst in Achondroplasia we observe only one infolding of the embryo, viz. the infolding of the embryonic axis, in Dysostosis Cleido-cranio-(digitalis) we observe two infoldings: one of the fœtal axis, another infolding of the transverse axis which passes through the shoulders. Our conception is as follows:

If in the eighth week the amnion remains too small, by direct pressure it brings the forehead of the fœtus into too intimate contact with the anterior surface of the trunk. The shoulders are displaced forward and squeezed against the ribs and eventually also the inferior part of the head. The clavicles (sometimes also a single clavicle) are folded. So direct pressure explains all the mechanical malformations we have enumerated, and even a number of others, such as the frequent depression shown by the sternum, and probably also the abnormal curve of the shoulder-blade and of the acromion, as well as the subluxation of the humerus which have been described.

If we apply the principles mentioned in the Introductory Note to the symptoms of retardation of growth in Dysostosis Cleido-cranio-(digitalis) which we have just enumerated, they at once lose their enigmatic character.

In the eighth week of fœtal life all parts which in Dysostosis are affected by retardation of development—the frontal bones, the clavicles, the intermediate and terminal phalanges of the toes—are still flexible, scleroblastematous or precartilaginous; but at the same time they are changing their consistency by becoming osseous (frontal bones, clavicles) or cartilaginous (intermediate and terminal phalanges). So *they are all in a condition of rapid growth.*

Whilst all other skeletal parts have just undergone this important change, these bones are at that time the only ones that change their consistency; hence also the only ones whose *rapidity of growth determines enhanced vulnerability.*

The fibrous covering of the brain is ossifying at the moment of infolding. The medial part of the forehead, prominent as it naturally is, must meet with the greatest pressure from the trunk. [The back part of the head, though meeting with the same direct pressure of the amniotic sac, distributes this pressure over a much larger area (cf. Postscript, last paragraph p. 82).] For the same reason the jugal or malar bones, forming a prominence, are more exposed than the surrounding parts. The skin

covering these parts is not affected. It does not happen to be in a condition of rapid development, as are the brainpan and the skeleton of the face, and so it does not change its conformation nor its consistency.

As regards the clavicles which are rapidly ossifying about the eighth week, we may assume that they are folded by the direct pressure which acts on the shoulders of the fœtus. In the fold normal nutrition is inevitably inhibited, and this part loses its power of growth, whilst the two other ends may continue developing, or else these medial and lateral parts of the clavicles are compressed inasmuch as they are scleroblastematous, and these also may lose their power of growth, so that they also may be absent in the adult; and the same may hold good of the cases of defective development of the shoulder-blade that have been described.

Whilst direct enhanced pressure of the amnion is evoking the mechanical deformities as well as retardation of growth in those parts which are most exposed to this pressure, and are at the same time growing most rapidly, pressure is also increased in the amniotic liquid. *Increased direct amniotic pressure is inevitably attended by increased indirect or hydrostatic pressure.* The cartilaginous skeleton has just formed, and is even dotted with bone-centres. Only the intermediate and terminal phalanges of the toes are precartilaginous. They are the last skeletal parts to change their scleroblastema into cartilage. (As is well known, the trunk first undergoes this change, next come the extremities, and the development of the posterior extremities always comes after the anterior.)

So whilst in the eighth week the cartilaginous condition of the skeleton protects the whole skeleton from compression by enhanced hydrostatic pressure, the terminal phalanges of the toes are still in a condition to suffer from it. Normal scleroblastema, in changing into cartilage, in a short lapse of time undergoes an expansion surpassing the original volume several times. For this reason the developing cartilage suffers first and most from famine, sooner and more, for instance, than the skin which enwraps it. From the condition of its terminal phalanges Dysostosis Cleido-cranio-(digitalis) thus appears as a late and partial form of Achondroplasia. If the symptoms apparent in skull and clavicles are evoked by enhanced direct amniotic pressure, those in the terminal phalanges are produced by enhanced indirect or hydrostatic amnion pressure.

It stands to reason that indirect or hydrostatic pressure of the amnion only evokes symmetrical symptoms, whilst direct pressure may cause asymmetrical symptoms. An asymmetric attitude of the fœtus in the amniotic sac might give rise to asymmetric infolding and asymmetric effects on the skull and clavicles, due to direct amnion pressure. But enhanced indirect or hydrostatic pressure would lead even then to a

symmetrical dwarfing of the terminal phalanges. In accordance with this we note that in our figures the terminal phalanges show symmetrical dwarfism, whilst the changes of skull and clavicles regularly show asymmetries. The probability must, of course, be considered that enhanced direct pressure of the amniotic sac may be added to symptoms due to indirect pressure and thus mask their symmetry. For all that the dwarf symptoms in Achondroplasia, as well as the effects on the terminal phalanges of Dysostosis, are of striking symmetry.

Summing up we find that in Dysostosis the symptoms of retardation of development in the skull and in the clavicles are associated with mechanical malformations. They even blend with them, thus furnishing further grounds for the assumption of a common cause—enhanced direct amniotic pressure. Moreover, these two groups of malformations lead us to the adoption of enhanced indirect or hydrostatic pressure acting at the same time and causing growth-stunting of the terminal phalanges.

Fitz-Williams and other authors have tried to represent Dysostosis Cleido-cranio-(digitalis) as an exclusive affection of the bones formed in membrane. The skeletal parts which develop in membrane start their ossification after the greater part of the rest of the skeleton has become cartilaginous. To us this difference in the time of ossification rather than a difference in the nature of the bones is to be considered as the cause of the predominant involvement of bones formed in membrane. The dwarfing of the intermediate and terminal phalanges, indeed, as well as the shortness of the long bones of the extremities, refute Fitz-Williams' view, and, even if we could admit that only the bones formed in membrane are affected, the cause of this growth-stunting is not explained by that author any more than is the cause of the mechanical malformations.

If we have succeeded in pointing out the relations between Dysostosis Cleido-cranio-(digitalis) and Achondroplasia, it will be easy to answer the different questions that may arise, as, for instance:

Why does Achondroplasia show signs of infolding not only in the head but also in the presence of a lumbodorsal arcuate kyphosis, whilst Dysostosis shows the infolding only in the head?—In the eighth fœtal week the trunk is cartilaginous (osseous even in some of its parts). At that moment it is far less flexible than in the fifth and sixth weeks, when its cartilage is only forming. And we have arguments to adduce[1] that for this reason the amnion in the seventh week loses its power of infolding the fœtus, and that after the seventh week the amnion is rather distended by the fœtus than the fœtus rolled up by the amnion.

[1] Cf. *Achondroplasia*, l.c., p. 65 ff.

Why is it that in Achondroplasia the extremities are most conspicuously dwarfed, whilst in Dysostosis Cleido-cranio-(digitalis) only the terminal phalanges of the feet show obvious stunting and the other bones of the extremities are often only doubtfully affected?—In the fifth and sixth week the entire skeleton of the extremities is scleroblastematous. Then all skeletal parts, owing to the enhanced hydrostatic pressure, meet with abnormal resistance to the increase of volume with which the transition into cartilage is associated. In the seventh week, the time of the origin of Mongoloid Idiocy, the dwarfing of the extremities is less obvious. By the eighth week the cartilage of the extremities has been largely formed except that of the peripheral parts. So at that time these are the only ones to expand and thus to meet with such resistance.

Why is Achondroplasia not attended by enlargement and late closure of the large fontanel?—By the fifth or sixth week the covering of the brain is still membranous. The ossific activity which determines the vulnerability, presents itself in the covering of the brain only about the eighth week.

Why are the clavicles not affected in Achondroplasia? Why does Achondroplasia not show the effects of transverse infolding?—By the fifth week the clavicles have not yet begun their development. The shoulders have not yet been formed. Only later on do the clavicles lengthen and constitute lateral prominences. Hence it is only then that they may be subjected to folding, displacement and compression.

If the relationship between Dysostosis and Achondroplasia has been made clear, it should be also noted that both conditions are often associated with other congenital malformations such as rachischisis, spina bifida, congenital clubfoot and many others. Achondroplasia has been observed to be attended by Mongoloid Idiocy, as Mongoloid Idiocy is constantly accompanied by symptoms of Achondroplasia (Dr. Van der Scheer). Briefly, Dysostosis and Achondroplasia appear to be related not only mutually, but also with a number of other congenital malformations, judging from the enhanced frequency with which these conditions occur either in Dysostotic or Achondroplasic subjects, as well as in members of their family.

There are two points left to which we must direct attention :

First there is the fact that the father of the subject of Fig. 3 (see Fig. 31) shows indisputable dwarfing of the extremities, whilst signs of infolding, *i. e.* of direct pressure, are missing both in trunk and skull. In our monograph on Achondroplasia, we have emphasized the fact that in Achondroplasia the dwarf-symptoms are not always proportional to

those of infolding, *i. e.* to the mechanical malformations. Though direct pressure, when increased, necessarily entails enhanced hydrostatic pressure, hydrostatic pressure in the amnion may be seriously enhanced without direct pressure necessarily making itself felt. This condition may be met in the case of hydramnios. Therefore the absence of signs of infolding in the subject of Fig. 31 is not in contradiction with our views. Among the dwarf-symptoms, on the contrary, there is one that may tend to confirm them: though the terminal phalanges of his feet

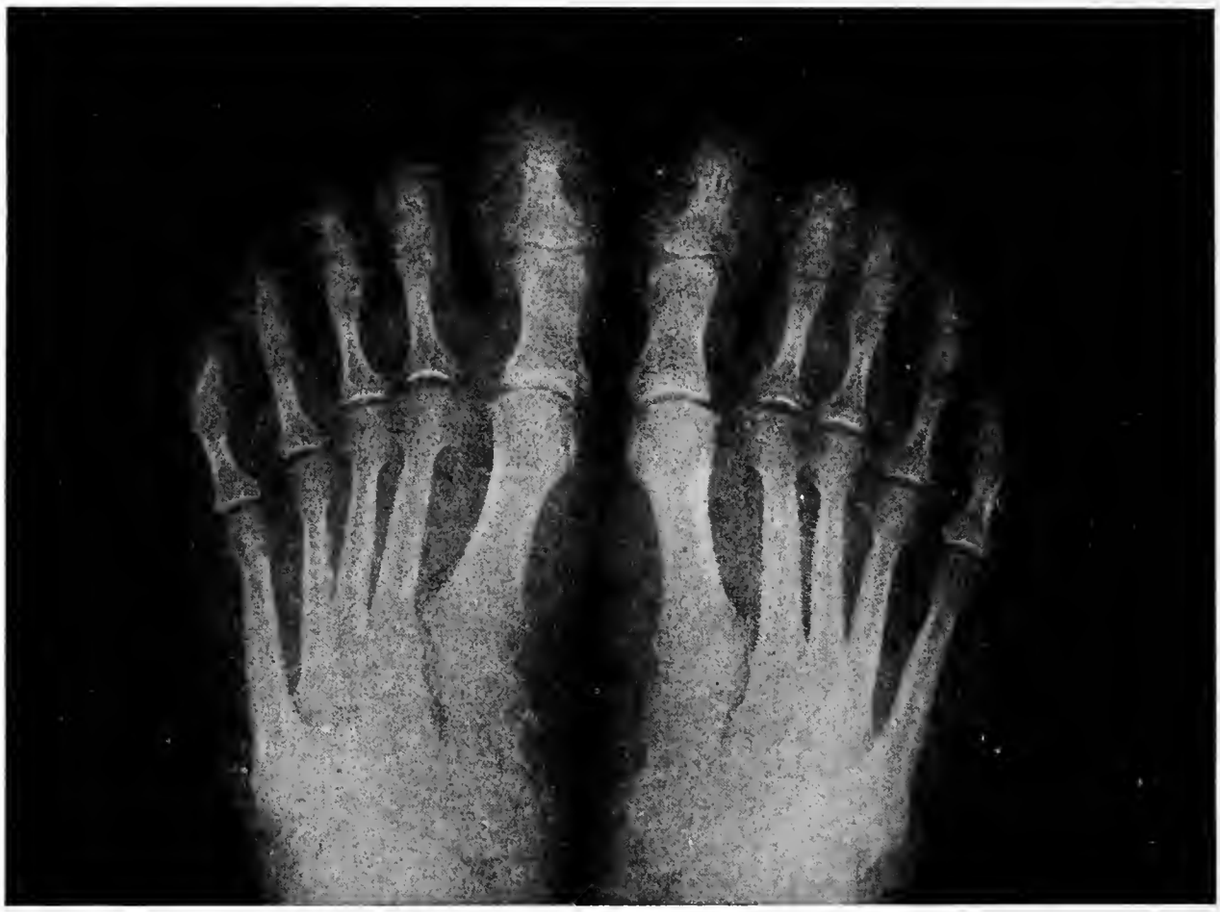


FIG. 35.—(Father Mev.) Father of the Dysostotic subject of Figs. 3 and 20. Non-dysostotic, yet showing "*Syndrome of the short extremities.*"

have their normally widened end, the intermediate phalanges show a shortness that we also observed in all our cases of Dysostosis; and that we have not observed—at least not in the same degree—in normal subjects (cf. Fig. 35 with Fig. 16).

This *coincidence of dwarfing of the extremities and the intermediate phalanges of the toes* apart from Dysostosis, is not unique. In Fig. 36 we represent a lady, and in Fig. 37 the skiagram of her feet, showing the same *syndrome of the short extremities.* It is a slight, late or partial form of Achondroplasia.

It is difficult to imagine that this syndrome, showing itself in the father of a Dysostotic subject, as well as in Dysostotic subjects themselves, should be independent of Dysostosis Cleido-cranio-(digitalis). It is much more plausible to ascribe it to the same cause, viz. enhanced hydrostatic pressure. The absence of signs of direct pressure then enforces the assumption that hydramnion, *i. e.* relative rather than absolute smallness of the amnion, has been at fault. And, if we do so,

FIG. 36.—(Mrs. Z.) Non-dysostotic, but showing "*Syndrome of the short extremities.*"

we seem to get more intimate information about the effect and operation of smallness of the amnion. In view of the fact, indeed, that the basal phalanges are properly developed and the widened ends of the terminal phalanges are also present, we are forced to assume that the increase of hydrostatic pressure has taken place a short time after the basal phalanges changed into cartilage and has been lowered before the ends of the terminal phalanges adopted their cartilaginous consistency. From this it would follow that enhanced hydrostatic pressure in these cases has lasted only a very short time, for hours rather than for days. It should be noted that in all probability this is nothing unusual. The very fact that

amnion pressure, for instance, which has evoked Achondroplasia, does not as a rule also produce the characteristic effects of pressure of later weeks, pleads in favour of the assumption that the smallness of the amniotic sac usually lasts only a short period. Here, of course, it may be argued that the Achondroplasic fœtus has adapted itself to the smallness of the sac. But the high frequency of undue deepening of the foveola coccygea in congenital clubfoot (as in other congenital malformations) equally pleads in favour of the assumption that smallness

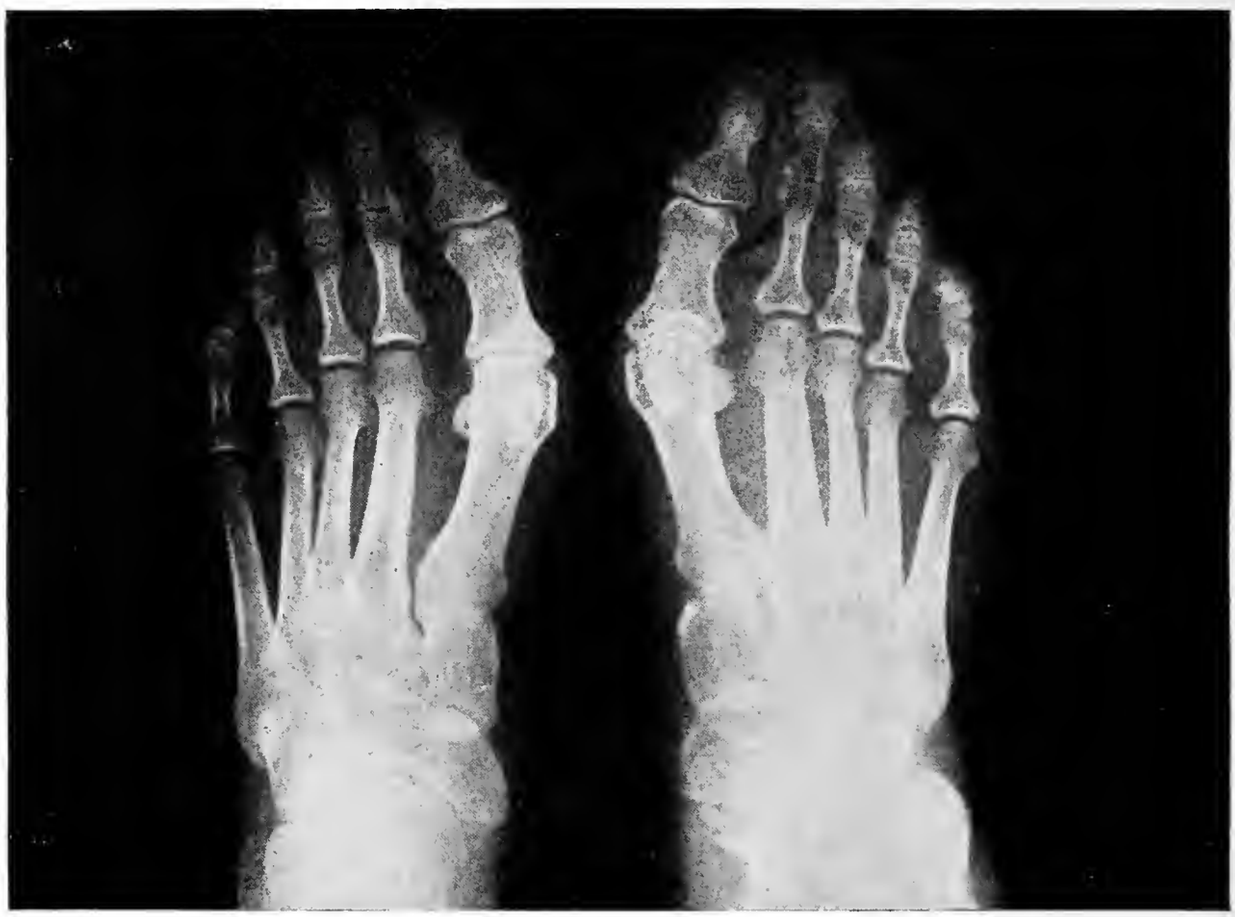


FIG. 37.—(Mrs. Z.) Non-dysostotic, but showing "*Syndrome of the short extremities.*"

of the amniotic sac may occur at an early age and soon disappear, and recur after a lapse of time without any perceptible sign of accommodation of the embryo to the smallness of the amniotic sac betweenwhiles.

Secondly, there is the *gigantism of two fingers* in Fig 38 (see also Figs. 39 and 40), who is a daughter of the Dysostotic mother of Fig. 4 and a sister of the Dysostotic subjects of Figs. 5, 6, 7 and 8. The missing finger has had to be amputated, because its size gave trouble. The contrast of this phenomenon with the numerous phenomena of retardation of growth which we have discussed in the family of this subject, makes it seem of a totally different nature. Yet we have reasons to assume

that there is a special affinity between this local gigantism and the local dwarfism we have just tried to explain. We have often observed symptoms of partial dwarfing (smallness of toes and metatarsals) and symptoms of gigantism (giant toes) in the same case of congenital club-foot. It is evident that if we wish to attribute these phenomena to smallness of the amnion, they can only have been caused by direct pressure—hydrostatic

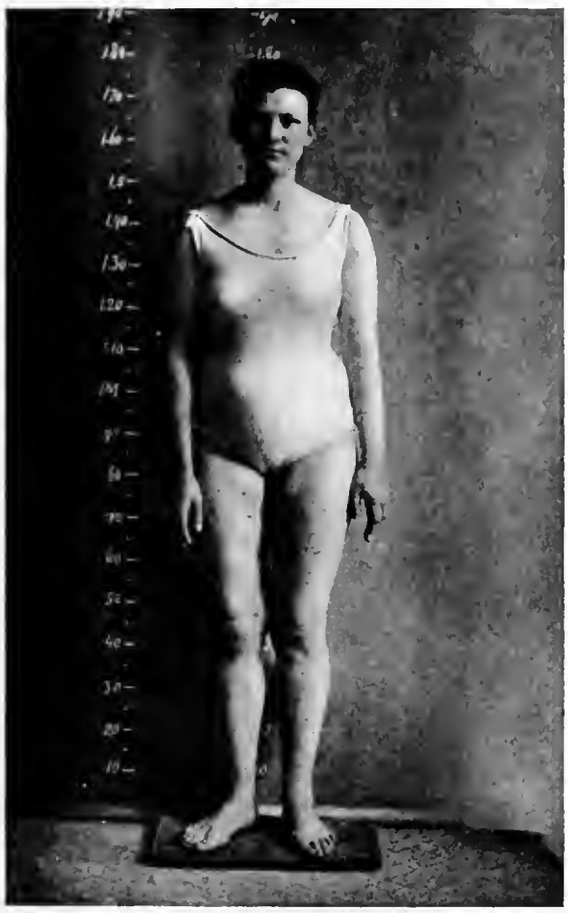


FIG. 38.—(L. Gro.) Non-dysostotic daughter of Dysostotic mother (Fig. 2), having four Dysostotic brothers and sisters (Figs. 3, 4, 5 and 6). Note giant fingers on left hand.

pressure always evoking symmetrical symptoms. Now it stands to reason that local pressure on flexible parts, when only slight, will first close veins only and still allow afflux of blood. Stasis must ensue as well as dilation of veins and even of arteries, which in its turn may be the cause of local gigantism. Stronger pressure, which compresses the arteries as well as the veins, may create local famine, from which local dwarfing or even death may ensue, if the Ischæmia is of sufficient intensity and duration. The giant finger of the subject of Fig. 38 therefore is not in real contradiction with the views we have tried to establish. On the contrary, it may

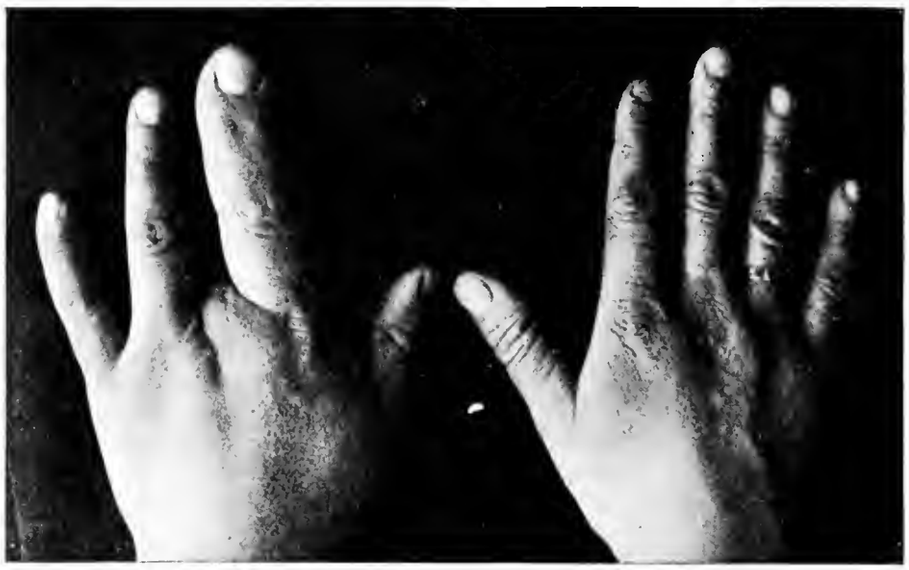


FIG. 39.—Hands of Fig. 38 (L. Gro.). Non-dysostotic.

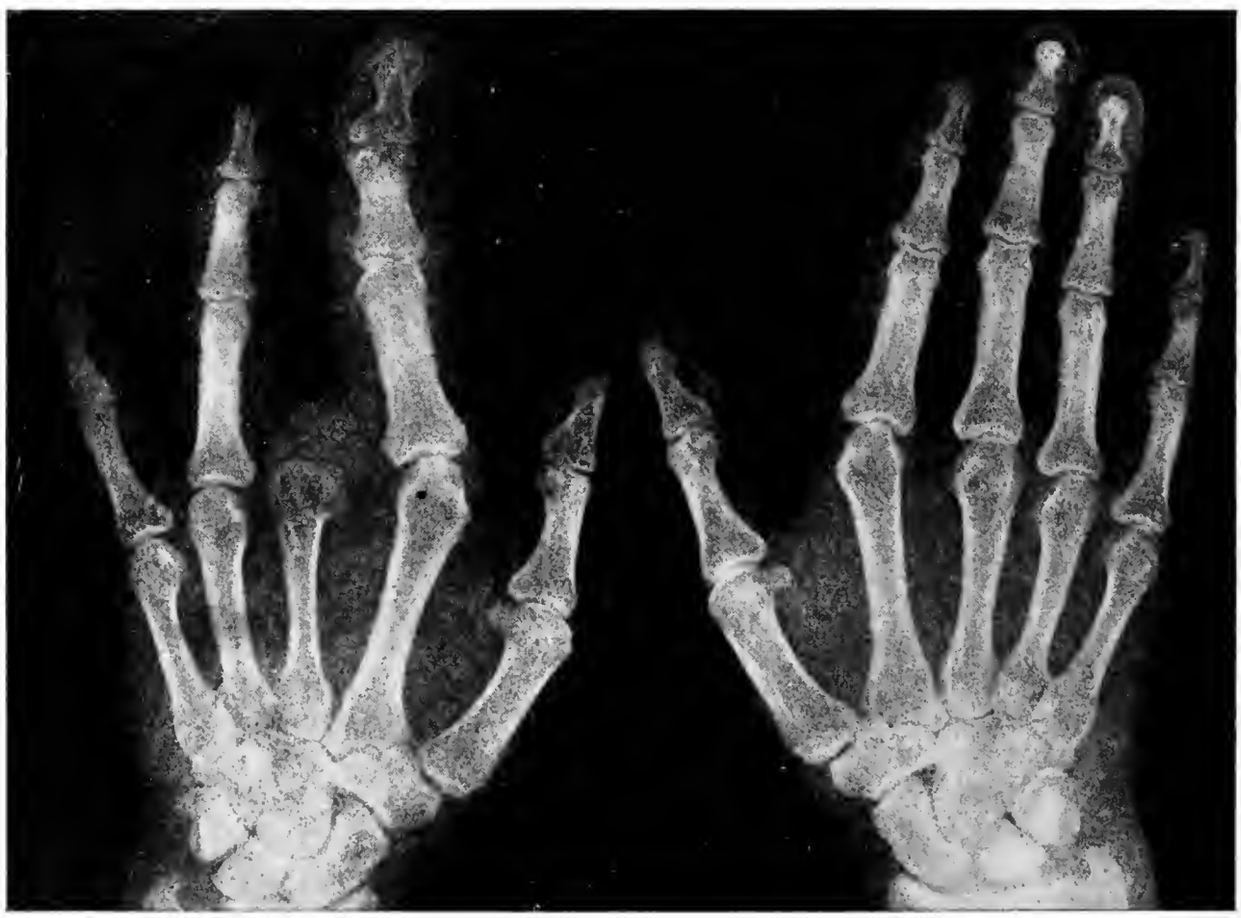


FIG. 40.—X-ray of hands of Fig. 38 (L. Gro.). Non-dysostotic.

be explained by the assumption that this subject has been affected by the direct pressure of too small an amnion as well as the dysostotic members of her family, possibly after the eighth week, since evident signs of dwarfing of the terminal phalanges and of infolding of the skull are missing. An unfavourable position of a hand in an amnion only a little too small (the pressure in that case being slight) might be the cause without any other symptoms being necessarily apparent.

CONGENITAL CLUB-FOOT AND CONGENITAL DISLOCATION OF HIP

After the eighth week, when the whole of the skeleton has adopted its firm consistency, the fœtus is protected from undue compression by the amniotic sac. This firmer consistency, the diminishing rapidity of growth and the fact that the different parts of the body, once having been formed, show more of a proportional increase in size—with exception of the extremities—may be made responsible for the dwarfing symptoms falling into the background. They are practically limited to the concave side of the mechanical deformity or may be missing altogether. Thus the great variety of malformations which the first two months of intrauterine life produce, makes room for more uniform mechanical changes.

The disproportionately rapid growth of the extremities after the eighth week surely makes them more vulnerable even then than the other parts, and our observations favour the view that at the beginning of the third month enhanced amniotic pressure may lead to a retardation both of the enchondral and the periosteal growth of the bones of the extremities. Be this as it may, there is no doubt but that some time after the eighth week amniotic pressure may lead to the formation of club-foot without dwarfing the extremities. This deformity is so far the only one that has been generally accepted to be the possible result of amniotic pressure :

(1) Because the feet of the newly-born club-footed child may be regularly readjusted so that their contours are suggestive of the spherical surface of their former enwrapments ; and

(2) On account of the vestiges of pressure which the thinness of the skin betrays at the most exposed part, viz. the dorsum of the foot.

Yet it is patent that these signs of pressure designate the amnion with less certainty as the cause of the deformity than do the conditions discussed in the above, which are attended by mechanical malformations of the body axis as well as by symmetrical dwarf symptoms, all of which far more imperatively claim for their explanation the simultaneous action of direct and indirect (= hydrostatic) pressure, such as can be ascribed to the amnion only.

Therefore a far stronger argument for the assumption that club-foot is a frequent result of amniotic pressure is that it so often accompanies the conditions dealt with in the above.

In a large number of club-footed subjects there is an antero-posterior shortening of the skull: the forehead is flattened as well as the occiput from the lambda upwards, as the stroking hand—if not the eye—may verify. They are evidently the earlier or the more serious cases.

Congenital club-feet, when associated with infolding of the body axis, show dwarfing of the extremities besides the deformation.

Club-feet in which one or more of the toes and corresponding metatarsals are missing, must obviously have their cause before the time at which these parts become cartilaginous.

In an admirable study Le Damany [1] has brought forward most plausible arguments for the assumption that amniotic pressure may be the cause of congenital dislocation of the hip. The pressure acting against the knees of the flexed legs, levers the femoral head out of its socket. The luxation and the never-failing anteversion of the femoral neck are the resulting deformities, together with the lengthening of the capsule and ligament. So in congenital dislocation of hip dwarf symptoms are missing altogether. The smallness of the bone-centre in the dislocated femoral head is indeed a retardation of differentiation, and thus of growth, well deserving attention. However, it tends to repair after normal functional pressure has been made to act by reduction. Hence this retardation of growth—of the third stage: differentiation—is due to the absence of functional pressure, and to be well distinguished from the real dwarfism, discussed in the previous sections, which is a permanent condition due to an active nocivity, viz. famine during growth.

In congenital dislocation of the hip again, the fact that it will run in families and alternate with conditions mentioned in the above, pleads in favour of their having a common cause.

POSTSCRIPT

If we have enumerated a series of misdeeds of amniotic pressure we are fully aware of having mentioned only a few of the most striking ones. From observations on Cyclopia made by Prof. Winkler it seems possible to us that this condition—and the whole series of transitions from Synotia to Cebocephaly—fits in between Anencephaly and Achondroplasia. Hitherto, however, we have not had an opportunity of examining subjects affected by these dwarfings before they had become deformed by the

[1] Le Damany, "Une nouvelle théorie pathogénique de la luxation congénitale de la hanche," *Revue de Chirurgie*, 1904, No. 2.

pressure from bottles with hardening liquids. So hints concerning the presence or absence of mechanical malformations in them are lacking; and we are looking forward to the examination of fresh specimens.

Besides these a large number of congenital malformations—as Spina bifida, Harelip, Micrognathy, and Agnathy, Myxœdema, Hydrocephalus, Hemi-ectromelia [1] and many others—have been left out of discussion, as well as the characteristic stiffness of joints with defective musculature due to outflow of the amniotic liquid, or changes due to amniotic bands, because it was not our aim to give a complete series of the misdeeds of the amnion, but only to work out the principles mentioned in the Introductory Note of this book.

Nor did we mean to exclude other causes from the production of congenital deformities. Parts other than the amnion may cause compression, and quite apart from pressure, any nocive agent may lead to dwarfism —as has been conclusively proved in experimental pathology.

For congenital deformities hereditary in the male line, the germ-cells are evidently to be made responsible, and if they are due to amniotic pressure, the "gemmule," "pangene," "plastidule," "determinant," "biophore," "ide" or whatever the small particle in the germ-cell destined for the production of the amnion, may be termed, has been defective at the moment of impregnation. In other cases which show no heredity, the amnion itself may have been injured by physical, chemical or microbic influences. Thus in the above varied series of congenital deformities the investigation of the cause has been reduced to that of an inquiry into the causes of slackened growth of the amnion.

It stands to reason that just as well as the "pangene" of the amnion that of any other organ may be affected by hereditary changes. But it must be emphasized that, before hereditary changes of "pangenes" of other organs may be assumed as the cause of any congenital deformity, the mechanical method of research followed in the above should be applied.

In the above we have directed attention to the fact that a change which is produced by pressure, acting for example in the fifth week, is only in the minority of cases associated also with conditions that would have been evoked by pressure in previous or following weeks: the Achondroplast is not necessarily also a Mongoloid Idiot. The undue pressure of too small an amniotic sac appears not to last the whole of fœtal life. This may, as we suggested, be due to the fact that the dwarfism of the parts means a relative increase to the size of the sac. But on the other hand, the hypothesis seems justified that the sac resumes its growth to the stimulus of pressure. It seems plausible that the amnion as well as

[1] Cf. *Achondroplasia*, l.c.

the brainpan normally grows *paru passu* with its contents, responding to the slightest pressure by rapidly providing the space needed. Smallness of the amnion would then mean retarded response to normal stimuli. But be this as it may, certain it is that the causation of dwarfism or even death of embryonic parts requires only a number of hours, not of days. Every clinician knows that only one night of ischæmia of living parts—compression of the skin between a bony surface on the inside and plaster or a hard mattress on the outside—kills the compressed parts, causing decubitus. Hence in the rapidly-growing fœtus the same length of time must be deemed sufficient to cause dwarfing or death of the parts.

To the conception of amniotic pressure causing deformities it has been objected that " amniotic pressure cannot deform the fœtus, since it acts evenly on all parts."—This holds good for hydrostatic pressure; not, however, for direct pressure. Suppose too small an amniotic sac to be in contact only with the head and the feet of the fœtus. During rest the pressure on the head is equal to that on the feet. The pressure-bearing surface being smaller, the pressure per unit of surface is greater. Hence the feet will sooner be deformed. The study of the deforming properties of too small an amniotic sac should be initiated by the knowledge of these and similar elementary physical truths.

SYN

SOME OF THE T

SMALLNESS O

Approximation of date :	Condition of the skeleton :	Parts of the embryo being distinguished by the rapidity of their growth :	B Mechanical r tions
± 2nd or 3rd week.	Mesoderm.	The head begins to develop.	Wrinkling embryonic axi
± 3rd or 4th week.	Scleroblastema.	The prechordal part of the head continues to outgrow previous proportions.	? (Not yet ex
± 5th or 6th week.	Cartilage forms.	The skeleton, becoming cartilaginous, enlarges several times.	Increase of cal infolding o skull.
± 7th week.	The skeleton of the extremities is becoming cartilaginous.	The skeleton of the extremities, continuing to become cartilaginous, and the brain, outgrowing previous proportions.	The trunk, come cartila longer allows infolded. The skull, trary, still a to be infolded.
± 8th week.	The skeleton is cartilaginous except the peripheral parts of the extremities. The cranial roof and the clavicles ossify.	The peripheral parts of the extremities, becoming cartilaginous, the skull and the clavicles ossifying and outgrowing previous proportions.	The cranial membranous, infolded. The which have veloped, may l forward.
After the 8th week.	The whole skeleton is cartilaginous or osseous.		The skull n tened antero-p the extremiti deformed or d

Note that ischæmia, evoked by amnion pressure at various times, each time strikes the p
Note also that local death is the privilege of the first weeks, local dwarfing of the later w

)PSIS

'ICAL MISDEEDS

THE AMNION

ENHANCED AMNION PRESSURE MAY CAUSE:			
)IRECT PRESSURE:		BY INDIRECT OR HYDROSTATIC PRESSURE:	Clinical name of the composite deformities:
forma-	Retardation or arrest of growth (local *dwarfism* or local *death*), not necessarily symmetrical:	Retardation or arrest of growth (local *dwarfism* or local *death*), necessarily symmetrical:	
f the	Local death of meso- and ectodermal parts of the head.		Anencephaly.
ined.)	Local death of meso- and ectodermal parts of the head.		Synotia. ↓ Cyclopia. ↓ Cebocephaly. } ?
siologi- nk and		Dwarfism of cartilaginous skeletal parts graduated according to the time of their development.	Achondroplasia.
ing be- us, no lf to be he con- s itself	Dwarfing of the brain (of the interpeduncular region).	Dwarfism of the peripheral of the extremities, chiefly of the terminal phalanges of the toes.	Mongoloid Idiocy (van der Scheer).
of, still may be oulders, st de- splaced	Retardation of development of the bones of the skull and of the clavicles.	Dwarfism of the terminal phalanges of the toes.	Dysostosis Cleido-cranio-(digitalis).
be flat- eriorly; nay be ated.	Dwarfism chiefly on the concave side of the mechanical malformations.		Congenital club-foot, congenital luxation of hip.

growing most rapidly (see 3rd column) with local death or dwarfism (5th and 6th column).